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VIRUS ISOLATION AND CHARACTERIZATION

1. FAMILIAL ACUTE MYELOGENOUS LEUKEMIA ASSOCIATED WITH RNA VIRUS AND POLYMORPHISM OF 1QH+.

Sadamori N, Nonaka H, Ichimaru M, Igarashi H, Hirota M, Sawada H

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Cancer Genet Cytogenet; 4(1):23-30 1981

In order to investigate the genetic background of leukemogenesis of two brothers with acute myelogenous leukemia (AML), they and their family members were studied genetically, immunologically, virologically, and cytogenetically. Their parents were first cousins once removed and had the same or a very close type of human WBC antigen (HLA) and blood groups. In all five non-leukemic family members the IgG level was elevated, and in two healthy siblings the IgM level was beyond the normal range. The RNA reverse transcriptase activity in serum of the younger brother (Case 2) with AML was elevated. A cytogenetic study of the family revealed polymor-

HE 20.3173/2:

phism of 1qh+. Based on these findings, we discuss the genetic and environmental factors of familial leukemia. (Author abstract) (24 Refs)

2. EARLY MOUSE EMBRYO INTRACISTERNAL PARTICLE: FOURTH TYPE OF RETROVIRUS-LIKE PARTICLE ASSOCIATED WITH THE MOUSE.

Yotsuyanagi Y, Szollosi D

Centre de Genetique Molecularie, Centre National de la Recherche Scientifique, 91190 Gif-sur-Yvette, France

JNCI; 67(3):677-685 1981

Electron microscopy combined with a quantitative analysis was used to study the virus-like particles appearing in oocytes and preimplantation embryos of nine mouse strains; inbred AKR, NZB, BALB/c, and C3H/He; randombred Swiss; inbred DDK; noninbred Peru; and ranombred Q and MF1. Main findings were as follows: (1) The omnipresence was noted in mice of a fourth type of retrovirus-like particle (referred to as epsilon-particle) clearly distinguishable from the known A-, B-, and C-type particles and resembling more closely the R-type particles of the hamster. (2) epsilon-particles occur transiently within the endoplasmic reticulum of early cleavage-stage embryos and have not yet been observed in either oocytes or later embryos, in normal adult tissues, or in tumors. (3) Intracisternal A-particles, identical to those seen generally in mouse tumors, also occurred in oocytes and early embryos but by far in smaller numbers than did epsilon-particles. (4) The production of epsilon- and A-particles exhibited exactly inverse patterns of developmental stage dependence. These patterns were basically similar, regardless of the mouse strain examined. (5) In contrast, the mode of occurrence of C-type particles was subject to a great strain-dependent variation. (Author abstract) (42 Refs)

3. INDUCTION OF TRANSFORMED PHENOTYPES IN SHEEP FIBROBLASTS BY CULTURE FLUIDS FROM CELLS PERSISTENTLY INFECTED WITH BOVINE LEUKEMIA VIRUS.

Onuma M, Watarai S, Suneya M, Mikami T, Izawa H

Dept. Epizootiology, Faculty Veterinary Medicine, Hokkaido Univ., Sapporo, Hokkaido 060, Japan

Microbiol Immunol; 25(5):445-454 1981

Transformation of sheep fibroblasts by incubation with culture fluids from bovine leukemia virus (BLV)-producing fetal lamb kidney (FLK) cells and calf-born bovine lymphosarcoma (3178) cells is reported. Inoculation of concentrated culture fluids from FLK and 3178 cells onto fibroblasts from testes of normal sheep produced a morphological transformation from fibroblast-like to epithelial-like cells; the changes were observed after the second or third passage. Syncytial assay showed the presence of BLV in all transformed cells, and electron microscopy revealed the presence of type C virus. Transplantation of virus-infected sheep fibroblasts produced tumor growth in athymic nude mice; the tumors had histology of fibrosarcoma. Transformed cells showed a 2.8-3.5x greater uptake of the glucose analog (2-deoxy-D-glucose) than control sheep fibroblasts. (24 Refs)

4. RNA-DIRECTED DNA POLYMERASE ACTIVITY IN HUMAN BREAST CANCER BIOPSY SPECIMENS (MEETING ABSTRACT).

Weiss GB, Carr BK, Rae-Venter B

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4th Annual San Antonio Breast Cancer Symposium, Nov 6-7, 1981, San Antonio, Texas Cancer Therapy and Research Center of South Texas; 1981

The possibility of a viral etiology of human breast cancer has been considered since 1936 when Bittner discovered that breast cancer in mice was related to a factor in milk. Type C viral particles and RNA-directed DNA polymerase (reverse transcriptase (RT) have both been detected in human breast cancer but the frequency and significance of these findings are unknown. Breast tumor biopsy specimens (from either the primary site or a metastasis) frozen in liquid nitrogen at the time of surgery were routinely obtained to determine estrogen receptor (ERP) concentration. A sample of the tissue was pulverized, homogenized and then centrifuged to remove nuclei and mitochondria. The supernatent was centrifuged at 250,000 x g to obtain the cytosol fraction for steroid receptor assays. Estrogen and progesterone receptors were assayed by the method of Jensen et al. Partially purified membranes for RT assay were prepared from the pellet by sucrose density gradient centrifugation. The RT assay involves measuring primer dependent poly (dT) synthesis in the presence of poly (A) as template and oligo (dT) 12-18 as primer. To date, we have studied tumors from 46 patients with breast cancer and found 28 (61%) to be RT positive. There was no significant correlation with ERP status with half of the RT positive being ERP positive. Progesterone receptor (PgR) data was available on only 31 of the patients; no correlation between RT and PgR is apparent. The RT assay is frequently positive in breast cancer and does not correlate with either ERP or PgR status. Correlation with survival and response to therapy is being determined prospectively. (no Refs)

5. HUMAN TERATOCARCINOMAS PRODUCE UNIQUE ONCOVIRUS-LIKE PARTICLES (MEETING ABSTRACT).

Kurth R, Lower J, Lower R, Wernicke D, Frank H

Max-Planck-Institute for Virus Research, Tubingen, W. Germany

RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

Among a series of human tumors investigated, only the five human teratocarcinoma cell lines derived from testicular tumors or pulmonary metastases of patients in Germany and the USA were shown to produce spontaneously virus-like particels, albeit in low yield. Morphologically, the particles are reminiscent of C-type oncoviruses which can cause tumors in animals. Production of the human te ratocarcinoma-derived (HTD-) particles can be increased by cellular selection in tissue culture and by chemical induction procedures which are known to increase the rate of oncovirus synthesis. The replication-defective HTD-particles can be distinguished from all known animal oncovirus strains by morphological, biological and immunological criteria. The endogenous or exogenous origin of the HTD-particles is not yet known, neither can it be decided at present whether they are in any way causally related to the etiology of teratocarcinomas or whether they represent passenger viruses. (no Refs)

6. HTLV, A TYPE-C VIRUS ISOLATED FROM HUMAN T-CELL MALIGNANCIES, IS T-CELL TROPIC (MEETING ABSTRACT).

Reitz M, Wainberg M, Ruscetti F, Ceccherini-Nelli L, Gallo RC

Laboratory of Tumor Cell Biology, National Cancer Institute, Bethesda, MD

RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

The isolation of type-C virus, HTLV, from the malignant T-lymphocytes of a patient (CR) with cutaneous T-cell lymphoma has been described. An identical or closely related virus was later isolated from the malignant T-lymphocytes of a second patient (MB) with another T-cell lymphoma-leukemia, Sezary syndrome. We report here that the maligant T-cells of both patients had viral sequences present in both RNA and DNA. DNA from these T-cells of patient CR contained 2-3 copies per haploid genome of HTLV provirus and 0.3-0.5% by wt of HTLV messenger RNA in total cytoplasmic RNA. In contrast, B-lymphocytes established in culture from this same patient had substantially less than one copy per haploid genome of HTLV provirus, and no HTLV RNA was detectable in cytoplasmic RNA. Purified HTLV labelled with 3H-uridine was used to determine if this apparent cellular specificity was a reflection of cellular restriction of viral entry and penetration. Autoradiography showed that viral RNA entered normal T-cells and persisted in the cytoplasm for two days, after which it was no longer detectable. When 3H-uridine labelled virus was mixed with normal T-cells, the label was releasable by trypsinization after 15' incubation at 37 degrees, but was completely resistant after 2 or 4 hr. Substantially less binding of radiolabelled HTLV was observed to B cells than T cells. These results suggest that HTLV has a tropism towards T-cells and is restricted by B-cells at the level of viral penetration. (2 Refs)

7. A XENOTROPIC VIRUS OF AKR ORIGIN THAT REPLICATES IN HUMAN CELLS (MEETING ABSTRACT).

Crowther R, Tenney D, Haseltine W

Sidney Farber Cancer Institute, Harvard Medical School, Boston, MA, 02115

RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

A cell line. SL11, derived from a spontaneous AKR mouse thymoma was the source of two types of xenotropic virus. Cocultivation of SL11 with dog 8155 cells yielded a xenotropic virus, SL11-X1, that replicates in dog, cat and mink but not human cells. The RNase T1 fingerprint of SL11-X1 is nearly identical to that of AKR-X6, and AKR xenotropic virus with an identical host range. Cocultivation of SLH with human RD cells yielded a xenotropic virus, SL11-X2, that replicates in human as well as dog, cat and mink cells. Comparison of RNase T1 fingerprint of SL11-X2 with SL11-X1 and Akv suggest that SL11-X2 did not arise by simple recombination between SL11-X1 or Akv with endogeous RD sequences. Thus, it is possible that two endogenous xenotropic viral loci exist in AKR tissues, one of which expresses a virus capable of growth in human cells. (no Refs)

8. STUDIES OF MYLV, A VIRUS THAT CAUSES ACUTE MYELOGENOUS LEUKEMIA IN C57BL MICE (MEETING ABSTRACT).

Salles J, Teich N, Rowe J

Imperial Cancer Research Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England

RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

At the present time, there is little biochemical or molecular information on the viruses that induce myeloid leukemias in mice. One such virus, MyLV, was isolated following numerous serial passages of a polycythemia strain of Friend erthroleukemia virus complex in Swiss and neonatal C57BL mice. The major pathological characteristic of this virus isolate is the induction of myelomonocytic leukemias, predominantly of chloroleukemic type, with no evidence for spleen focus forming activity of for lymphatic and/or erythroid leukemia induction. Inoculation of MyLV into neonatal BALB/c mice induces a disease similar to that caused by the Friend helper virus, ie, severe anemia and hepatosplenomegaly. However, markedly WBC counts are also observed. Attempts to characterize the virus further include biological cloning and analysis of viral structural proteins by sodium dodecyl sulfate polyacrylamide gel electophoresis. In the regard, we can identify two replication competent viruses. It seems likely that one of these viruses may represent the original Friend helper virus and that the second may be the oncogenic myeloid agent which acts alone or in concert with the other competent virus. We have also isolated several non producer cell clones which synthesize gPr85env and gp70 but do not make any gag related products; thus, they may just represent gag mutants. Furthermore, neither the uncloned parental stock nor the clonal isolates synthesize gp55, the recombinant env gene protein encoded by the spleen focus forming virus component of Friend virus complex. (no Refs)

9. STUDIES OF BSB, A VIRUS THAT CAUSES ERYTHROLEUKEMIA IN C57BL MICE (MEETING ABSTRACT).

Teich N, Rowe J

Imperial Cancer Research Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3 PX, England

RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

The polycythemia and anemia inducing strains of Friend erythroleukemia virus complex do not produce erythroleukemia in C57BL mice, primarily due to the effect of the Fv-2rr gene. However, by blind passage of the polycythemia strain in neonatal C57BL mice, a new variant (BSB) capable of inducing erythroleukemia and spleen foci in C57BL mice was developed. Our preliminary investigation of the BSB stock by sodium dodecyl sulfate-polyacrylamide gel electrophoresis indicated a very complex pattern of intracellular virus specific proteins, compatible with the idea of multiple virus components. Thus, we undertook to separate the different entities by endpoint dilution and single cell cloning. The protein patterns of the cell clones showed marked diversity as well: both replication competent viruses and replication defective viruses fell into several distinct classes. These results suggest the occurrence of more than 3 viral components, and perhaps also the emergence of mutants and/or variants. Neither the uncloned BSB nor the cloned derivatives synthesize gp55, the env gene recombinant protein considered the hallmark of the erythroleukemia inducing replication defective spleen focus forming virus component of Friend virus complex. The replication competent viruses, as well as replication defective components rescued by superinfection with various helper viruses, are being analyzed for tumorigenicity in neonatal and adult mice. (no Refs)

VIRUS ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

10. AVIAN RETICULOENDOTHELIOSIS VIRUS: IDENTIFICATION OF THE HEMATOPOIETIC TARGET CELL FOR TRANSFORMATION.

Lewis RB, McClure J, Rup B, Niesel DW, Garry RF, Hoelzer JD, Nazerian K, Bose HR
Dept. Microbiology, Univ. Texas, Austin, TX, 78712
Cell; 25(2):421-431 1981

Non-virus-producing hematopoietic cells transformed in vitro by reticuloendotheliosis virus (REV-T) induced lethal 'reticuloendotheliosis' when inoculated into histocompatible chickens. This is the first direct demonstration that an in vivo target cell of an avian acute leukemia virus can be transformed in vitro. The tumorigenic, REV-T-transformed non-virus-producing cells fail to express helper-virus-coded proteins. REV-T-transformed tumorigenic cells therefore do not require helper-virus functions. Cells transformed in vivo or in vitro by REV-T have lymphoblastoid morphology and express low levels of terminal-deoxynucleotidyl-transferase activity and bursal-cell determinants. One clone synthesized Ig u. The preferred target cells for REV-T transformation are therefore immature lymphoid cells that express B-cell determinants. We propose that the unique transforming sequence of REV-T be designated rel (lymphoid). (Author abstract) (56 Refs)

11. LEUKEMOGENIC PROPERTIES OF AKR DUALTROPIC (MCF) VIRUSES: AMPLIFICATION OF MURINE LEUKEMIA VIRUS-RELATED ANTIGENS ON THYMOCYTES AND ACCELERATION OF LEUKEMIA DEVELOPMENT IN AKR MICE.

O'Donnell PV, Stockert E, Obata Y, Old LJ
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Virology; 112(2):548-563 1981

The late preleukemic period in AKR mice (6-8 mo of age) is characterized by amplified expression of murine leukemia virus (MuLV)-related cell surface antigens on thymocytes. Analysis of thymic biopsies of preleukemic AKR mice at 180 days of age showed that antigen amplification was prognostic of spontaneous leukemia development within approx 100 days. In the present study we have investigated the viral basis of this preleukemic change in AKR thymus. Cloned isolates of ecotropic, xenotropic, and dualtropic MuLV that were derived from preleukemic or leukemic AKR thymus were tested by intrathymic injection of young AKR mice to determine which of the three classes of MuLV could induce antigen amplification, and, subsequently, accelerate leukemia development in the same animal. Only dualtropic MuLV exhibited these two activities in vivo. Considerable heterogeneity was observed among the 13 dualtropic MuLV isolates examined. In vitro three distinct serological phenotypes could be recognized on the basis of expression of MuLV gag gene-coded antigens GCSA and MuLV env gene-coded antigens GIX, G(RADA1), G(ERLD), and G(AKSL2) on the surface of infected cells. Virus isolates also differed in (i) relative ecotropic-xenotropic host range (dualtropism) as assayed by ratios of infectious titers on mouse and mink cells, (ii) induction of mink cell foci (MCF), and (iii) infectivity for NIH/3T3 cells.In vivo the two activities of antigen amplification and leukemia acceleration could be dissociated and thus represent distinct virus phenotypes. Seven isolates of dualtropic MuLV induced antigen amplification; these viruses encoded GIX, G(ERLD), and G(AKSL2) antigens, were MCF inducing, had SC-1/mink titer ratios of 0.4 or greater, and were infectious for NIH/3T3 cells. Only three of these virus isolates (MCF 247, MCF 69L1, and MCF 13) accelerated leukemia development. Analysis of dose-response relationships and kinetics of virus-induced antigen amplification by MCF 69L1 virus implicated virus infection of thymocytes in the preleukemic change. Moreover, the level of MuLV antigen expression on thymocytes at approx 1 mo postinjection of MCF 69L1 virus correlated directly with development of early leukemia. It is apparent that leukemia development in young AKR mice which can be induced experimentally by intrathymic injection of cloned isolates of dualtropic MuLV exhibits the hallmarks of spontaneous disease in this strain and thus can serve as a useful model for study of thymic leukemogene sis in mice. (Author abstract) (55 Refs)

12. WILD MOUSE ECOTROPIC MURINE LEUKEMIA VIRUS INFECTION OF INBRED MICE: DUAL-TROPIC VIRUS EXPRESSION PRECEDES THE ONSET OF PARALYSIS AND LYMPHOMA.

Hoffman PM, Davidson WF, Ruscetti SK, Chused TM, Morse HC
Veterans Admin. Medical Center, Dept. Neurology, Basic and Clinical Immunology and Microbiology, Medical Univ. South Carolina, Charleston, SC, 29545
J Virol; 39(2):597-602 1981

NFS/N mice inoculated at birth with an ecotropic murine leukemia virus (Cas-Br-M MuLV) obtained from wild mice developed hind limb paralysis beginning at 7 wk of age and nonthymic lymphomas beginning at more than 20 wk of age. Studies of 1-to 7-wk-old Cas-Br-M MuLV-infected mice showed the following: (i) a marked increase in nonecotropic MuLV-related antigens on spleen cells but not thymocytes beginning at 2 wk; (ii) the appearance of dual-tropic mink cell focus-forming (MCF) MuLV-related gp70 in spleen but not thymus or brain cells at 4 wk; and (iii) the isolation of infectious MCF MuLV from spleen cells of 7-wk-old mice. A role for MCF MuLV in Cas-Br-M MuLV-induced nonthymic lymphomas is indicated by these studies, and a role for recombinant MuLV in neurological disease is considered. (Author abstract) (22 Refs)

13. FELINE UVEAL MELANOMAS INDUCED WITH FELINE SARCOMA VIRUS: POTENTIAL MODEL OF THE HUMAN COUNTERPART.

Shadduck JA, Albert DM, Niederkorn JY
Dept. Veterinary Pathobiology, Coll. Veterinary Medicine, Univ. Illinois, Urbana, IL, 61801
JNCI; 67(3):619-627 1981

Uveal melanomas were produced by injecting Gardner strain feline fibrosarcoma virus intraocularly into 10-to 15-day-old noninbred kittens. Tumors developed in about 90% of the cats' eyes receiving virus. Progressing tumors (62 eyes of 36 cats) began as small hyperpigmented lesions at the site of injection and grew to fill the anterior chamber by 3-5 mo after infection. About 30% of cats with these tumors developed secondary tumors and died. Nonprogressive tumors characterized by flat, pigmented plaques on the iris at the site of injection developed in 25 eyes of 18 cats. These lesions did not enlarge except in proportion to the growth of the eye. Tumors were composed of pigmented spindle cells, pigmented epithelioid cells, and nonpigmented spindle cells. The cells could be grown for five-eight passages in vitro. One culture assumed a transformed morphology and grew in noninbred athymic nu/nu mice. The lesions resembled human spindle cell melanomas. (Author abstract) (24 Refs)

14. ISOLATION OF TRANSPLANTABLE ERYTHROLEUKEMIA CELLS FROM MICE INFECTED WITH HELPER-INDEPENDENT FRIEND MURINE LEUKEMIA VIRUS.

Oliff A, Ruscetti S, Douglass EC, Scolnick E
LTVG, NCI, NIH, Building 41, Room D-240, Bethesda, MD, 20205
Blood; 58(2):244-254 1981

The Friend virus complex contains a helper-independent retrovirus, F-MuLV, and a replication-defective retrovirus, SFFV. Murine erythroleukemia cell lines (MEL) have been isolated previously from the leukemic tissues of mice infected with such stocks of Friend virus complex. Since our laboratory has shown that either F-MuLV or SFFV can induce a lethal erythroproliferative disease, it has been unclear which of the properties of conventional MEL cells were causally related to the infection of these cells by F-MuLV and which properties were related to the infection of these cells by SFFV. In this article, we have focused on the helper-independent component of the Friend virus complex, F-MuLV clone 57, which has recently been purified by molecular cloning. We report a method for the reproducible isolation of a new type of murine erythroleukemia cell that can be isolated from mice infected with F-MuLV clone 57. We have designated these cells as 57 TP-1, indicating their origin from mice infected with F-MuLV clone 57 and their characteristics as transplantable erythroleukemia cells. Upon sc, ip, or iv inoculation of these cells, 57 TP-1 cells grow in the hematopoietic organs of the recipient mice. No sc or ip nodules occur. Both F-MuLV and a Friend MCF virus can be detected in these cells, but no evidence of SFFV can be found. (Author abstract) (26 Refs)

15. CLONAL ANALYSIS OF THE LATE STAGES OF ERYTHROLEUKEMIA INDUCED BY TWO DISTINCT STRAINS OF FRIEND LEUKEMIA VIRUS.

Mager D, MacDonald ME, Robson IB, Mak TW1, Bernstein A1
Lab. Genetics, Univ. Wisconsin, Madison, WI, 53706
Mol Cell Biol; 1(8):721-730 1981

Differences between the tumorigenic colony-forming cells in the spleen of DBA/2J mice late after infection with the anemia-inducing strain of Friend leukemia virus (strain FV-A) and those present after infection with the polycythemia-inducing strain (FV-P) were explored. Hb and spectrin was found in cells within primary colonies derived from FV-A- and FV-P-transformed cells (CFU-FV-A and CFU-FV-P), suggesting that the CFU-FV-A and CFU-FV-P were transformed erythroid progenitor cells. In newly isolated cell lines from colonies of CFU-FV-P colonies, more than 25% of the cells contained Hb, while only 0-2% of cells from CFU-FV-A colonies contained Hb. In response to pure erythropoietin, many cells derived from CFU-FV-A colonies accumulated spectrin and Hb, while cell lines derived from CFU-FV-P did not. Primary CFU-FV-P colonies were diploid, while chromosomal aberrations were observed in the immediate progeny of CFU-FV-A. It is suggested that individual colonies from CFU-FV-A originated from single cells. Leukemic progenitor cells transformed by strain FV-A had the capacity to self-renew, while many of the corresponding cells transformed by FV-P did not, and as the disease progressed, the capacity of both strains to self-renew increased. A model for the multistage nature of Friend disease is proposed. (51 Refs)

16. SECRETION OF A VIRUS-REGULATED FACTOR BY CLONAL VARIANTS OF RETICULOENDOTHELIOSIS VIRUS-TRANSFORMED HEMATOPOIETIC CELLS.

Garry RF, Bose HR
(c/o Bose) Dept. Microbiology, Univ. Texas, Austin, Austin, TX, 78712
Virology; 113(1):403-407 1981

Reticuloendotheliosis virus (REV-T) is an avian acute leukemia virus which transforms hematopoietic cells which express bursal cell determinants in vivo and in vitro. REV-T-transformed hematopoietic cell lines spontaneously give rise to stable variants that secrete a factor which results in the formation of a halo surrounding colonies formed in soft agar. Expression of this phenotype does not correlate with helper virus production, growth rate or morphology, secretion of immunoglobulin, or the tumorigenic potential of the cells. The secretion of this factor appears to be regulated by the genetic information of REV-T. (Author abstract) (9 Refs)

17. TRANSFORMATION-ENHANCING FACTOR(S) RELEASED FROM CHICKEN ROUS SARCOMA CELLS: EFFECT ON SOME TRANSFORMATION PARAMETERS.

Kryceve-Martinerie C, Biquard JM, Lawrence D, Vigier P, Barlati S, Mignatti P
Faculte des Sciences, Institut Curie (Biologie), 91405 Orsay, France
Virology; 112(2):436-449 1981

The medium of chick embryo fibroblasts (CEF) transformed by Schmidt-Ruppin strain of Rous sarcoma virus (SR-RSV) contains a factor(s) which complements the expression of some transformation parameters depending on the src gene. Notably, it reverses the block by puromycin of morphological transformation of cells infected with three ts-T mutants after shift-down from restrictive (41.5 C) to permissive (37 C) temperature. This reversal is not due to the release of inhibition of protein synthesis produced by puromycin, and is accompanied by the expression of two other src-dependent transformation parameters: disorganization of the cytoskeleton and loss of cell surface-associated fibronectin. The factor(s) able to overcome the puromycin block of morphological transformation was operationally called transformation-enhancing factor (TEF) like a previously reported factor favoring transformation by RSV. It is lacking in media of untransformed cells, uninfected or infected with a nontransforming virus (RAV-1), and its production by RSV-infected cells seems to depend on the acquisition of the transformed phenotype, therefore on the expression of the src gene. Its effect was also shown to persist beyond the period of contact with the cells. It appears to be a glycoprotein which can be resolved by gel filtration into two peaks of 250K and 190K, apparently distinct from other known factors spontaneously released by transformed cells. A similar activity was also found in the medium of mammalian (rodent) cells transformed by SR-RSV and by other RNA and DNA oncogenic viruses, but not in the medium of untransformed controls. (Author abstract) (38 Refs)

18. INHIBITORY EFFECT OF A REVERTANT CELL ON IN VIVO GROWTH OF ITS PARENTAL TRANSFORMED CELL LINE.

Ebbesen P, Olsson L
Inst. Cancer Res., Danish Cancer Society, Radium stationen, DK-8000 Aarhus C, Denmark

J Cancer Res Clin Oncol; 100(3):329-332 1981

The in vivo effects of revertant and normal cells on the growth of transformed cells were studied using two revertant cell lines, KSR-4111 and KSR-12121, cloned from a sarcoma virus-transformed non-virus producing murine 3T3 cell line, K-BALB-23. Grafting of KSR-4111 at the site of tumor cell grafting significantly reduced the incidence of histologically verified takes, while inoculation at a distance from the graft was ineffective. Tumor development was not influenced by KSR-12121 or the normal 3T3 cells, and none of the cell lines influenced growth of the two mammary tumors. Grafting of two syngeneic mammary tumors was not affected by the presence of the protective revertant cells. KSR-4111 was further characterized by inducing cytotoxic non-theta-antigen-bearing spleen lymphocytes in grafted syngeneic recipients. (10 Refs)

19. HYALURONATE-PROTEIN COMPLEX OF ROUS SARCOMA VIRUS-TRANSFORMED CHICK EMBRYO FIBROBLASTS.

Mikuni-Takagaki Y, Toole BP
(c/o Toole) Dept. Anatomy and Cellular Biology, Tufts Univ. Sch. Medicine, Boston, MA, 02111

J Biol Chem; 256(16):8463-8469 1981

Involvement of covalently linked protein or peptide in the structure or synthesis of hyaluronate has not previously been convincingly demonstrated. We have developed conditions for double-labeling with [3H]leucine and [14C]acetate, then isolating and characterizing the cell-associated and secreted hyaluronate-protein complexes of Rous sarcoma virus-transformed chick embryo fibroblasts. The preparations were purified by Bio-Gel A-15m gel filtration and CsCl density gradient ultracentrifugation under dissociative conditions, followed by acid agarose gel electrophoresis in the presence of 0.1% Nonidet P-40. The purified hyaluronate preparations did not change their 3H:14C ratios after further sodium dodecyl sulfate or alkali treatment. The cell-derived hyaluronate-protein was resistant to pronase but susceptible to proteinase K in the presence of sodium dodecyl sulfate. After chondroitinase ABC digestion, the cell-derived 3H-labeled protein was separated from the 14C-labeled hyaluronate disaccharides, then shown to give a broad band corresponding to Mr approx = 12,000 on sodium dodecyl sulfate-urea polyacrylamide gel electrophoresis and to be susceptible to both pronase and proteinase K. The corresponding 3H-labeled peptide was prepared in the same manner from the medium hyaluronate and the [3H]leucine shown to be present in material smaller in amount and size than that from the cell. We propose from these and other published data that the cell-associated hyaluronate-protein may be bound to the cell surface and that the hyaluronate in the medium may be derived from it as a result of proteolytic scission. (Author abstract) (48 Refs)

20. UPTAKE OF 5'-DEOXY-5'-S-ISOBUTYL THIOADENOSINE INTO CHICK EMBRYO FIBROBLASTS.

Enouf J, Lawrence F, Robert-Gero M
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Biochem Pharmacol; 30(15):2081-2087 1981

The uptake of 5'-deoxy-5'-S-isobutyl thioadenosine (iBuS)5' Ado into chick embryo fibroblasts is due to a mixed transport system: (1) a high affinity system with apparent Km values of 0.022 mM and 0.055 mM for normal and Rous Sarcoma Virus transformed cells respectively; (2) a low affinity system with apparent Km values of 0.800 mM and 0.720 mM for the normal and transformed cells. The drug enters the cells rapidly, and is found in the acid-soluble fraction. Only analogues of (iBuS)5' Ado modified in the 5'-S-side chain are found to be inhibitors of the high affinity system. This indicates that an intact adenosine is required. 2'-Deoxyglucose and factors affecting the cell membrane reduce the (iBuS)5' Ado uptake. (Author abstract) (41 Refs)

21. PHOSPHORYLATION OF RIBOSOMAL PROTEIN S6 IN AVIAN SARCOMA VIRUS-TRANSFORMED CHICKEN EMBRYO FIBROBLASTS.

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Proc Natl Acad Sci USA; 78(7,part2):4112-4115 1981

Protein phosphorylation was examined in whole cell extracts from normal and avian sarcoma virus-transformed chicken embryo fibroblasts. The addition of serum or epidermal growth factor to serum-starved normal cells resulted in increased 32P labeling of a Mr 30,000 protein. In extracts from cells transformed by a temperature-sensitive mutant of Schmidt-Ruppin virus, subgroup A, and grown at the permissive temperature, the protein was phosphorylated regardless of serum starvation. This Mr 30,000 protein was shown to be ribosomal protein S6, and the effects of avian sarcoma virus transformation on S6 phosphorylation were further investigated. The ability to phosphorylate S6 in the absence of serum was found to be temperature sensitive when S6 preparations from the temperature-sensitive mutant-infected cells incubated at permissive and nonpermissive temperatures were compared. Cells transformed by the parent virus (Schmidt-Ruppin, subgroup A) maintained the ability to phosphorylate S6 in the absence of serum when incubated at either temperature. Phosphoserine was the only phospho-amino acid detected in acid hydrolysates from phosphorylated S6 preparations. (Author abstract) (20 Refs)

22. LOCALIZATION OF THE ABELSON MURINE LEUKEMIA VIRUS PROTEIN IN A DETERGENT INSOLUBLE MATRIX: ARCHITECTURE OF THE PROTEIN (MEETING ABSTRACT).

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RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

Abelson murine leukemia virus (A-MuLV) encodes a 120,000 mol wt protein called P120. P120 is a phosphorylated surface membrane protein, which when incubated with 32P-ATP following immunoprecipitation becomes labeled with 32P on tyrosine residues. We have studied the interaction of P120 with other cellular components following extraction with the non-ionic detergents Triton X-100. Most of the A-MuLV P120 associated kinase activity was found with the detergent insoluble matrix (DIM) of both lymphoid and fibroblast cell lines. However, studies of the distribution of the 35S-methionine and 32PO(4)-labeled protein revealed a more complex pattern. P120 labeled during a short period of exposure of cells to 35S-methionine was mainly in the DIM (lymphoid cells) or equally distributed in the DIM and the soluble fractions (fibroblasts). Steady state labeled P120 was distributed equally in the two fractions (lymphoid cells) or mostly in the soluble portion (fibroblasts). Thus there was an apparent movement of P120 from the DIM to the detergent soluble fraction. When the DIM was incubated with 32P-ATP in situ, phosphorylation of tyrosine residues of P120 was observed. An 80,000 mol wt fragment of P120 (F80) was found after extraction of fibroblastic cells with detergent. F80 was not found in extracted lymphoid cells but mixing labeled lymphoid cells and unlabeled fibroblasts before extraction produced the fragment. F80 contained the gag determinants of p120 but did not react with Abelson-specific serum. (no Refs)

23. IDENTIFICATION OF AN ABELSON MURINE LEUKEMIA VIRUS-ENCODED PROTEIN RELATED TO P120 ON THE PLASMA MEMBRANE OF TRANSFORMED LYMPHOID CELLS (MEETING ABSTRACT).

Machida C, Kabat D
Departments of Microbiology and Immunology, University of Oregon Health Sciences Center, Portland, OR
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

A lymphoid cell line (L1-2) transformed by Abelson murine leukemia virus (A-MuLV) contains two virus-encoded proteins - p120 plus a small amount of a structurally related protein with an apparent Mr of 95,000 (p95). A novel surface detection technique suggests that p95, but not p120, occurs on the outer surface of cellular plasma membranes. This molecule is both immunologically and structurally related to A-MuLV p120, containing the gag related regions, p15 and p12, and limited portions of the unique 'x' host-encoded region. The p95 molecule is detected on the surface of this A-MuLV transformed lymphoid cell line only with tumor regressor serum recognizing this unique 'x' determinant. Tryptic peptide analysis of [35S] methionine-labeled proteins shows that p95 contains at least 7 peptides found in p120. Immunoprecipitated p95 can become phosphorylated in vitro by incubation with [gamma-32P] ATP and has been shown to contain the tyrosine-containing phosphorylation site previously described for p120. These results suggest that p120 may occur at intracellular site(s) in A-MuLV transformed cells. (no Refs)

24. IDENTIFYING TARGET OF PP60SRC USING PARTIAL TRANSFORMATION MUTANTS OF ROUS SARCOMA VIRUS (MEETING ABSTRACT).

Nakamura KD, Martinez R, Weber MJ
Department of Microbiology, University of Illinois, Urbana, IL, 61801
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

We have isolated and characterized mutants of Rous sarcoma virus (RSV) which induce some parameters of transformation, but fail to fully induce other parameters. Using these mutants, it is possible to correlate the appearance of specific parameters of transformation with the phosphorylation of specific proteins. For example, a protein with a nominal mol wt of 36,000 Daltons is phosphorylated on a tyrosine in Rous-transformed cells, and represents a major phosphotyrosine-containing protein in transformed cells. Phosphorylation of this protein is temperature-conditional in cells infected with tsNY68, a RSV mutant which is temperature conditional for all the measured parameters of transformation. The 36K protein is phosphorylated in cell infected with tsCuII, a mutant which does not greatly alter the morphology of infected cells, and it is heavily phosphorylated in cells infected with CU12, a mutant which does not cause complete loss of fibronectin. Cell infected with GI251 are thermo-sensitive for most parameters of transformation, but cold-sensitive for growth in soft agar. In cells infected with this mutant, the phosphorylation of the 36K protein is thermo-sensitive. Thus, phosphorylation of 36K does not correlate with morphological alterations, loss of growth control or loss of fibronectin. Of the parameters measured it correlates with increased glucose transport. (no Refs)

25. LOCALIZATION OF PP 36K, THE PRESUMED TARGET PROTEIN FOR THE SRC PROTEIN KINASE OF ROUS SARCOMA VIRUS, TO THE MEMBRANE OF CHICKEN CELLS TRANSFORMED BY ROUS SARCOMA VIRUS (MEETING ABSTRACT).

Amini S, Kaji A
Department of Microbiology, School of Medicine, University of Pennsylvania, Philadelphia, PA
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

The intracellular location of 36K protein in chicken embryo fibroblasts transformed by SR-RSV-A has been investigated using cell fractionation technique. In these studies 2-dimensional electrophoresis was used for the detection of phosphoproteins in the total cell extract and also in fractionated subcellular components. Our data suggest that PP 36 (phosphorylated form of 36 K protein) is associated with membrane in transformed cells radiolabeled in vivo with 32P-inorganic phosphate. The 36 K protein was not phosphorylated by in situ incubation of intact transformed cells with gamma-32P-ATP, whereas other membrane proteins were labeled. On the other hand the membrane fraction from transformed cell, upon incubation with gamma-32P-ATP in vitro, gave phosphorylated 36 K protein. We conclude that phosphorylated 36 K was well as non-phosphorylated 36 K, and src proteins must be localized in cellular membranes. These observations are also consistent with the proposed notion that src protein is not exposed to the outside of the cell. (no Refs)

26. PRESENCE OF RECOMBINANT MULV LIKE GLYCOPROTEIN IN VIRUS FREE MOUSE LYMPHOMAS: A MODEL FOR AUTOSTIMULATORY BLASTOGENESIS (MEETING ABSTRACT).

Fischinger P, Thiel H, Ihle J, Dunlop N
National Cancer Institute, Frederick, MD
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

The NIXT x-ray induced T-cell lymphoma line from Swiss mice had no virus or viral antigens detected by standard infectious assays or by radioimmunoassay or immunofluorescence (IFA) assays. However 5-10% of these cells in log phase of growth expressed on their surface in IFA an antigen reactive with anti VL-3 Rad LV gp70 serum which was primarily reactive with recombinant (RM) Murine leukemia viruses (MuLV). Ecotropic MuLV replicated in NIXT cells, but RM-MuLV could neither replicate nor enter these cells as seen by exclusion of Mouse sarcoma virus (MSV) (RM-) pseudotypes. Radioimmune precipitation tests of surface labeled cells with both anti VL-3 gp70 and other MuLV group reactive gp70 sera demonstrated a gp70, which by peptide maps was shown to be of the RM-MuLV class. This antigen may have a model role in leukemogenesis, because T lineage cells exist which have receptors for RM gp70, which when bound could act as a blastogenesis signal. The expression of permuted gp70's in the absence of virus on cell with receptors could result in continued cycles of replication. Thus, besides the direct onc gene product model, and the indirect promoter insertion model, one can postulate an alternate hypothesis based on the calls for clonal expansion of a receptor defined cell subpopulation. (no Refs)

27. A CHEMICALLY SYNTHESIZED PEPTIDE FRAGMENT CONTAINING THE ACTIVE TYROSINE OF RSVPP60SRC ALLOWS IMMUNOLOGICAL STUDIES ON THE SRC GENE ACTIVITIES IN TRANSFORMED CELLS (MEETING ABSTRACT).

Sen A, Neil JC, Ghuysdael J, Vogt PK, Lerner RA
Cellular Biology and Immunopathology Departments, Scripps Clinic and Research Foundation, La Jolla, CA
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, NY. Cold Spring Harbor Laboratory 294 pp., 1981.

A sequence of 10 amino acids, representing residues 413 through 422 which include the actigve tyrosine of the product of the SRC gene of RSV, has been chemically synthesized by the Merrifield procedure. Rabbit antisera have been generated against this fragment of the pp60SRC by immunizing animals with the synthetic peptide coupled to a carrier protein (KLH) through a cystine residue. This antipeptide serum has been used in direct immunoprecipitation of metabolically labelled p60SRC product from rat or chicken cells transformed by various strains of RSV. This serum, like an authentic anti p60SRC serum, also immunoprecipitates a protein kinase from RSV transformed rat or chicken cells but not from their normal parents. In vitro incubation of immunecomplexes obtained under less stringent conditions from transformed cell lysates using this serum results in the phosphorylation of an approx 80K protein this has not been observed with anti p60SRC serum. The phosphorylation of a protein of the same mobility is also seen in immunecomplexes formed from a murine sarcoma virus transformed rat cell line. The synthetic peptide contains the major tyrosine phosphorylation site of pp60SRC and falls inside the domain of homology between the murine SRC gene (MOS) product and the RSV pp60SRC, although this peptide is not present in the MOS gene product. (1 Ref)

28. CONTROL OF DIFFERENTIATED CELL FUNCTIONS BY ROUS SARCOMA VIRUS IN INFECTED CHICKEN CHONDROBLASTS (MEETING ABSTRACT).

Boettiger D, Pacifici M, Holtzer H, Adams S
Department of Microbiology, Anatomy and Human Genetics, University of Pennsylvania, Philadelphia, PA
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

Chicken embryo chondroblasts were obtained from 11 day embryonic vertebral columns and cultured as pure chondroblasts. These cells were infected with ts LA24A and grown at permissive temperature. RNA extracted from cells infected by ts LA24A or control cell growing at 36 degrees or 41 degrees was analyzed by in vitro translation. Infected cells growing at 36 degrees exhibited a decrease level of pro alpha 1 Type 2 collagen and increases in pro alpha 1 type and pro alpha 2 Type 1 collagen chains. A 450K protein which appears to be the core protein for the chondroblast specific proteoglycan and a 48K protein tentatively identified as link protein for sulfated proteoglycan were also decreased by cell transformation. The majority of differences seen in the in vitro translation system could be assigned to specific differentiated cell products, mostly extracellular matrix components. This contrasts with work in other systems in which a large number of differences were seen following cell transformation. Some of the changes observed upon transformation parallel those observed under culture conditions which lead to a loss of the normal differentiated cell phenotype. These results indicate that (1) src can affect synthesis of differentiated cell function at the m-RNA level, (2) both switch-on and switch-off of differentiated functions can be observed, (3) functions reduced or switched off by src in fibroblasts may be switched on or increased by src in chondroblasts, (4) cell transformation may affect only a small number of functions when uniform cell populations are used and degeneration of the normal program is minimized. (no Refs)

29. EFFECT OF CELL DIFFERENTIATION ON EXPRESSION OF ROUS SARCOMA VIRAL GENES (MEETING ABSTRACT).

Hsia K, Kaji A
Department of Microbiology, University of Pennsylvania, Philadelphia, PA
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

When mononucleated replicating chicken myogenic cells are infected with class T temperature sensitive Rous sarcoma virus (RSV) and incubated at nonpermissive temperature, normal multinucleated myotubes can be developed in cell culture. We define these myotubes as 'early infected myotubes'. Transformation of these myotubes can be observed morphologically upon temperature shift-down to permissive temperature, as the result of src gene expression. These 'late infected myotubes' remain unaffected morphologically even at 4 days post infection. Examination of viral proteins synthesized in these 'late' infected myotube cultures revealed comparable synthesis of gag proteins as well as pol precursor proteins as compared to those in infected fibroblasts; but the relative amount of env precursor (gPr92) and src (P60) proteins are significantly reduced. Normal synthesis of gPr92env and P60src was observed, however, in 'early' infected myotubes at both permissive and nonpermissive temperatures. Examination of the virion particles released from late infected myotube cultures revealed a significantly low ratio of FFU titer per unit virion gag proteins, as compared to those released from infected fibroblast cultures. These studies suggest that normal viral gene expression could be observed in myotube cultures when infection is at the stage of mononucleated, replicating, myogenic cells. However, when infection takes place at the stage of post-mitotic, terminally differentiated myotube cultures, viral gene expression becomes differential: the proteins synthesized from subgenomic sizes of viral RNA (env and src) were significantly reduced. This defective synthesis of env proteins would result in the production of defective particles from these cultures. (1 Ref)

30. GENE EXPRESSION PATHWAYS ALTERED IN VIRUS-TRANSFORMED CAT CELLS (MEETING ABSTRAC T).

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Sloan-Kettering Institute for Cancer Research, New York, NY
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

We have identified 3 transformed cat cell lines with unusual patterns of antigen expression. The cells failed to express a large block of cytoplasmic and membrane antigens which are charcteristic of both lymphocytes and fibroblasts. One of these cells, Null-VP1, was experimentally derived from a population of FLF3 fibroblasts transformed by the Snyder-Theilen strain of FeSV(FeLV) (Feline Sarcoma Virus with its Feline Leukemia Virus helper). The other two cells, Null-VP2 and Null-VP3, were derived from multiple lymphosarcomas of the cat were FeLV-positive, and were presumably transformed by this virus. All cells express feline oncornavirus associated cell membrane antigen, the FeLV- and FeSV-specific membrane antigen, and produce infectious virus. Characterization of the Null-VP cells was made possible by the development of a series of monoclonal antibodies to normal 'tissue-specific' feline antigens. These antigens are expressed only in cells of the adult cat descended from the embroyonic mesodermal germ layer, which includes both connective tissue cells (fibroblasts), and hematopoietic cells (WBC). We assume that a relatively rare event associated with the integration of FeLV (or FeSV) resulted in an altered expression of the regulator gene at this control point, resulting in the cessation of normal gene expression in these cells. (no Refs)

31. TRANSFORMATION OF HEMOPOIETIC CELLS IN VITRO BY HARVEY AND KIRSTEN SARCOMA VIRUSES (MEETING ABSTRACT).

Hankins WD, Scolnick EM
National Cancer Institute, Bethesda, MD
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

Infection of hemopoietic cells in vitro with the erythroleukemia-inducing Friend and Rauscher virus complexes induces these cells to proliferate and differentiate to form clusters of hemoglobinized colonies ('erythroid bursts') without addition of the hormone, erythropoietin (EPO). Maximal virus-induced burst formation occurred between 4-6 days post-infection. Pseudotype and kinetic studies indicated that the inducing agent in these preparations was the replication-defective spleen focus forming virus (SFFV). We report here that Harvey (HaSV) and Kirsten (KiSV) sarcoma viruses, which transform fibroblasts in vitro and cause erythroleukemia in vivo, also induce erythroid transformation in vitro. The erythroid bursts induced by HaSV and KiSV were virus dose-dependent, appeared 6-8 days post-infection, and were generally larger than those induced by SFFV. While burst formation occurred without added EPO, addition of minute amounts of the hormone markedly increased the number of bursts and the degree of hemoglobinization. Sin ce the burst-inducing activity was (1) heat labile; (2) inactivated by UV-irradiation; (3) removed by sedimentation of 100,000 x g; (4) genetically restricted at the Fv-1 locus; and (5) not found in KiSV and HaSV non-producer supernatants, it was most likely due to virus and not a soluble factor. (no Refs)

32. CHARACTERIZATION OF FBJ MURINE OSTEOSARCOMA VIRUS TRANSFORMED NONPRODUCER CELLS AND IDENTIFICATION OF A TRANSFORMATION SPECIFIC 39,000 DALTON PROTEIN (MEETING ABSTRACT).

Curran T, Teich N
Department of Viral-mediated Differentiation, Imperial Cancer Research Fund Laboratories, London, England
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

FBJ is complex of non-leukemogenic helpher virus (FBJ-MULV) and a replication defective osteosarcoma inducing murine sarcoma virus (FBJ-MSV). FBJ-MSV nonproducer rat cell clones have been obtained by low multiplicity infection and isolation of transformants in soft agar. No MLV-related antigens can be precipitated from these cells using antisera raised against disrupted helper virus. The nonproducer cells were used to induce tumors in syngeneic Fischer rats and also in (Wistar x Fischer) F1 rats. Sera from a number of these rats specifically precipitate a 39,000 dalton protein (p39) from FBJ-transformed producer and nonproducer cells. The peptide map of this protein is distinct from those of the structural proteins of the FBJ-MLV and the precipitation of p39 cannot be blocked by excess virion proteins. Antisera against this putative oncogene product do not precipitate the Kirsten-MSV oncogene product (p21) from Kirsten-MSV transformed cells nor any specific protein from Moloney-MSV transformed cells. We have also found that sera from a large number of rats, including uninjected controls, precipitate p15E and gPr90env from virus producing cells. The origin and significance of this activity are unclear. (no Refs)

VIRUS REPLICATION AND EXPRESSION

33. SELECTION OF RAT HEPATOMA CELLS DEFECTIVE IN HORMONE-REGULATED PRODUCTION OF MOUSE MAMMARY TUMOR VIRUS RNA.

Grove JR, Ringold GM
Dept. Pharmacology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Proc Natl Acad Sci USA; 78(7,part2):4349-4353 1981

We have been studying the mechanism of glucocorticoid hormone action by using mouse mammary tumor virus (MMTV)-infected rat hepatoma cells as a model system. J2. 17, a clonal cell line that contains one MMTV provirus, induces tyrosine aminotransferase (TyrATase; L-tyrosine:2-oxoglutarate amino-transferase, EC2.6.1.5), viral RNA, and the cell surface viral glycoprotein gp52 in response to dexamethasone. Using a fluorescence-activated cell sorter and a rabbit antiserum directed against gp52, we selected a cell population that displays a reduced hormone-mediated increase in cell surface gp5 2. Fourteen clones of this population were assayed for induction of viral gp52 and RNA and of cellular TyrATase. The results of these assays revealed that the clones display a variety of responses to hormone. One clone has retained wild-type responses of both TyrATase and gp52. Six clones exhibit coordinately reduced or abolished responses of both markers. Seven clones show normal induction of TyrATase but reduced or undetectable induction of gp52. These latter clones exhibit reduced production of MMTV RNA and thus may represent a unique class of variants defective in the regulation of MMTV gene expression. (Author abstract) (36 Refs)

34. IMMUNOSELECTION AND CHARACTERIZATION OF MOLONEY MURINE LEUKEMIA VIRUS-INFECTED CELL LINES DEFICIENT IN SURFACE GAG ANTIGEN EXPRESSION.

Edwards SA, Fan H
Peptide Biology Lab., Salk Inst., San Diego, CA, 92138
Virology; 113(1):95-108 1981

NIH/3T3 cells infected with Moloney murine leukemia virus (M-MuLV) which were deficient in gag surface antigen were selected by incubation with anti-serum to the major gag virion protein, p30, in the presence of complement. Survivors of the selection were cloned and characterized with respect to intracellular production of gag and env gene products, gag surface antigen expression as revealed by indirect immunofluorescence, and virus production. Nineteen clones tested were all positive for env gene products in cytoplasmic extracts. Seventeen of the 19 were positive for gag gene products, and 2 were negative. The gag-positive clones all produced Pr65gag (the precursor to the internal structural proteins) and they also produced gPr80gag (the precursor to the cell-surface gag antigen). The selected clones were all deficient in the presence of surface gag antigen as measured by immunofluorescent microscopy or flow microfluorimetry, and they all processed Pr65gag to mature p30 more slowly than the parental cells. In addition, all of the surface gag-deficient clones produced virus at a reduced rate. The nature of the defect in one gag-deficient clone was studied by infection of progeny virus onto uninfected NIH/3T3 cells. The resultant cells showed normal gag surface fluorescence and virus production. This suggests that the defect was cellular rather than viral. (Author abstract) (27 Refs)

35. EXPRESSION OF MURINE LEUKEMIA VIRUSES IN THE HIGHLY LYMPHOMATOUS BXH-2 RECOMBINANT INBRED MOUSE STRAIN.

Bedigian HG, Taylor BA, Meier H
Jackson Lab., Bar Harbor, ME, 04609
J Virol; 39(2):632-640 1981

Among 12 recombinant inbred strains of mice derived from crossing two strains, C57BL/6J and C3H/HeJ, which have a low incidence of neoplastic disease, one strain (BXH-2) has been found to have a high incidence of lymphoma, of non-T-cell origin, at an early age. The BXH-2 strain carries the Fv-1b allele and spontaneously expresses a B-tropic murine leukemia virus beginning at as early as 10 days of gestation and continuing throughout their life. No significant differences in ecotropic virus titers were observed at any age tested (16 to 17 days of gestation through 7 mo), whereas xenotropic virus was first detected in lymphoid tissues of 2-mo-old mice and virus titers increased with age. Dual tropic virus(es), which induced cytopathic changes on mink lung cells, was isolated from BXH-2 lymphomatous tissues. Unlike AKR mink lung focus-forming virus (N-tropic recombinant), BXH-2 dual tropic virus is B tropic and induces cytopathic changes in mouse fibroblast cultures as well. The BXH-2 mouse provides a model system for studying the role of replication-competent viruses in spontaneously occurring leukemias of non-T-cell lineage and neurological disease. (Author abstract) (38 Refs)

36. A MOUSE CELL LINE, WHICH IS UNPROTECTED BY INTERFERON AGAINST LYTIC VIRUS INFECTION, LACKS RIBONUCLEASE F ACTIVITY.

Epstein DA, Czarniecki W, Jacobsen H, Friedman RM, Panet A
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Eur J Biochem; 118(1):9-15 1981

A mouse cell line, NIH 3T3, does not respond to some of the activities of interferon. Even after treatment with high concentrations of interferon the replication of lytic viruses, such as encephalomyocarditis virus (EMCV) and vesicular stomatitis virus (VSV) is not inhibited in these cells. In contrast, interferon treatment of these same cells results in the inhibition of Moloney murine leukemia virus (MMuLV) production. We have analyzed enzymatic pathways which are induced by interferon in these cells. After interferon treatment, the level of the (2'-5')oligoadenylate [(2'-5')An] synthetase activity and the phosphorylation of the 67,000-dalton protein (P1) are enhanced in NIH 3T3 cells to approx the same level as interferon-sensitive mouse L-cells. Moreover, NIH 3T3 and L-cells contain approx the same levels of enzymes which inactivate (2'-5')An. Both exogenously added (2'-5')A3 or double-stranded RNA (dsRNA) failed to inhibit protein synthesis in NIH 3T3 extracts even though they were potent inhibitors of L-cell extract-directed protein synthesis. Direct measurements of the (2'-5')An-dependent ribonuclease F (RNase F) failed to detect such activity in NIH 3T3 cells. Our results, therefore, suggest that the presence of RNase F activity is necessary for the interferon-induced antiviral activity against EMCV and against VSV. The induction of protein kinase activity by interferon treatment of NIH 3T3 cells appears to have no direct effect on EMCV and VSV replication. (Author abstract) (44 Refs)

37. ELECTRON-MICROSCOPIC MORPHOLOGY OF VIRUS REPLICATION IN CELLS OF THE MURINE BORSTEL-LEUKEMIA X 429.

Fasske E, Fetting R, Themann H, Schopper C
Dept. Pathology, Borstel Res. Inst., Parkallee 1-40, D-2061 Borstel, W. Germany
J Cancer Res Clin Oncol; 100(3):263-270 1981

The morphologically evident steps of viral synthesis in cells of the Borstel-leukemia X429, induced by 200 rads of whole-body x-irradiation and cell-free transplantation in NMRI strain mice, were investigated. After ip injection of cell-free filtrates of X 429, leukemia developed in 21-22% of mice. The mean duration between injection and the appearance of the leukemia was 12.8 mo. Electron microscopy was used to study virus replication in the newly formed leukemia cells, with particular attention given to the relation between A-particles and mature type-C particles. Both intracisternal and intracytoplasmic A-particles were seen consisting of two concentric spherical shells with an external diameter of 70 nanometers. The A-particles were found mainly in cells or cell zones well endowed with membranes. Type-C viruses were formed externally on the outer cell membrane or on intracytoplasmic membranes by condensation of crescent-shaped electron-dense zones. After the virus detaches from the cell it collapses, and the outer membrane appears wrinkled. No spatial correlation between the storage sites of the A-particles and the sites of formation of mature type-C viruses were seen. (15 Refs)

38. RNA ONCOVIRUS EXPRESSION IN N-METHYL-N-NITROSOUREA-INDUCED LYMPHOMAS IN MICE.

Pinter A, Borzsonyi M
Natl. Inst. Hygiene, Budapest, Hungary
Int J Cancer; 28(2):219-223 1981

RNA oncovirus expression was investigated in thymic lymphomas induced by N-methyl-N-nitrosourea (MNU) in (C57BL/6 x DBA/2)F1(BDF1) mice. Out of 15 newborn mice injected with 20 mg/kg MNU, five developed thymic tumors of T-cell origin. Virus production of thymic cells from tumorous and normal animals was studied by an infectious center assay. All five tumors released ecotropic (mouse tropic) virus. No xenotropic or dual-tropic mink cell focus-inducing virus was found. No virus was obtained from thymus cells taken from six normal mice killed between 83 and 124 days; however, an ecotropic virus was cultured from the thymus of a 134-day-old normal mouse. According to these results, the MNU-induced thymic lymphoma development in BDF1 mice is accompanied by activation of endogenous ecotropic virus, whereas spontaneous activation also occurs in older mice. (Author abstract) (23 Refs)

39. ESTABLISHMENT OF CULTURED DD/TBR MOUSE MAMMARY TUMOR CELL LINES.

Iwai Y
Central Res. Inst., Radiation Center of Osaka Prefecture, Osaka, Japan
Nara Igaku Zasshi; 32(2):168-180 1981

Three mouse mammary gland cultured cell lines were established from a mammary carcinoma that spontaneously occurred in a 10-mo-old female DD/Tbr strain mouse. Two of the cell lines were epithelial (DD-762 and DD-763) type cells and one was spindle-shaped (DD-761). Except for the DD-764 cell line, the chromosome number was 80 and the population doubling time was 18 hr. These cell lines were thought to produce B-type RNA virus (MuMTV) and not murine leukemia virus (MuLV). Study of viral kinetics by means of RNA-directed DNA polymerase (RDDP) activity assay indicated that MuMTV production was observable during the stationary phase but not the logarithmic phase of cell growth. The production of the mammary tumor virus was found to be inversely dependent upon the presence of dexamethasone (DXM); MuMTV was produced in large amounts (0.8 mg viral protein/liter/day in DD-764), and the production was enhanced with the addition of DXM. (27 Refs) (In JPN)

40. ESTABLISHMENT AND PROPAGATION OF A BOVINE LEUKAEMIA VIRUS-PRODUCING CELL LINE DERIVED FROM THE LEUKOCYTES OF A LEUKEMIC COW.

Mamoun RZ, Astier T, Guillemain B
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J Gen Virol; 54(part2):357-365 1981

A cell line (LB59Ly) derived from the WBC of a leukemic cow was established as a monolayer, which spontaneously released large amounts of a retrovirus. This virus was found to be indistinguishable from the bovine leukemia virus (BLV) produced by the commonly used high-producing heterologous cell line (FLK-BLV). Like the latter, its reverse transcriptase activity was greater in the presence of Mg++ cations than in the presence of Mn++ cations; its polyacrylamide gel electrophoresis pattern showed the presence of gp51, p24, p15, p12 and p10, and the antigenicity of the two major proteins completely cross-reacted with those of BLV from FLK-BLV cells. the virus was infectious and induced early and late polykaryocytosis, the specificity of which was demonstrated by use of specific anti-BLV sera. (Author abstract) (26 Refs)

41. MILK OF DAIRY COWS FREQUENTLY CONTAINS A LEUKEMOGENIC VIRUS.

Ferrer JF, Kenyon SJ, Gupta P
Univ. Pennsylvania Sch. Veterinary Medicine, New Bolton Center, Kennett Square, PA, 19348
Science; 213(4511):1014-1016 1981

Milk or viable milk cells collected from 24 dairy cattle naturally infected with bovine leukemia virus were inoculated into lambs, which were subsequently examined for the development of infection. With this bioassay, infectious virus was demonstrated in the milk of 17 of the cows. Bovine leukemia virus is leukemogenic in at least two mammalian species, is widespread in commercial dairy herds, and can infect a wide range of hosts in vivo and cells, including human cells, in vitro. (Author abstract) (25 Refs)

42. AMPLIFICATION OF MULV-RELATED ANTIGENS ON PRELEUKEMIC AKR THYMOCYTES REPRESENTS EXPRESSION OF ENV GENE PRODUCTS ENCODED BY AN INFECTING DUALTROPIC (MCF) MULV GENOME (MEETING ABSTRACT).

O'Donnell PV, Nowinski RC, Stockert E
Sloan-Kettering Cancer Center, New York, NY, 10021
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

Several isolates of recombinant, dualtropic (MCF) Murine leukemia virus (MuLV) can induce the preleukemic change of MuLV antigen-amplification (A+) in thymocytes of young AKR mice and, subsequently, can accelerate leukemia development (L+) in these same animals. Unclear is (1) whether antigen-amplification represents expression of env gene products of the imput virus on the surface of infected thymocytes, (2) whether other endogenous env gene sequences are induced or (3) whether additional env gene recombinational events occur and are responsible for the amplication phenotype of premalignant thymocytes. Infection by antigenically-marked viruses has allowed us to decide between these alternatives. We have found AKR MCF isolates 247, 69L1, and 13 which are A+L+ can be distinguished serologically by specific patterns reactivity with mouse and rat monoclonal antibodies that recognize 10 distinct epitopes of AKR ecotropic MuLV gp70 and p15(E) proteins. Accordingly, 1 mo old AKR mice were injected intrathymically with either MCF 247, 69L1, or 13 viruses of tissue culture medium as control. Thymocytes of injected mice were assayed for amplification of specific epitopes at 30-35 d post-injection. Antigen expression was determined by quantitative membrane immunofluorescence with the fluorescence-activated cell sorter. The patterns of reactivity with monoclonal antibodies which were originally determined for each virus by immunofluorescent staining of infected mink cells in vitro were found to breed true on thymocytes infected in vivo. (no Refs)

3. TWO MURINE LEUKEMIA VIRUS PROTEIN KINASE ACTIVITIES AND THEIR POSSIBLE FUNCTIONS (MEETING ABSTRACT).

Yoshinaka Y, Luftig RB
Department of Microbiology and Immunology, University of South Carolina School of Medicine, Columbia, SC, 29208
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

Using an in vitro phosphorylation assay with detergent treated virus or core subparticles as substrate, we have found that: (1) Murine leukemia viruses, as avian leukemia viruses contain two protein kinase activities; one is preferentially acidic protein-accepting and the other prefers basic protein substrates. These can be separated by Sepharose 6B column chromatography. (2) The murine acidic kinase activity preferentially phosphorylates (80%) Pr65gag, in contrast to other virion proteins. In vitro phosphorylation of Pr65gag probably occurs at the p12 site since, when such Pr65gag is cleared in vitro, it produces as its initial product a band that has the Mr of Pr65gag and the antigenic determinants of p15 and p12. These results also indicate that the uncleaved Pr65gag packaged into virions is relatively unphosphorylated and is consistent with the contention of Naso et al that if Pr65gag is phosphorylated in vivo it is rapidly cleaved (3) The basic murine kinase activity preferentially phosphorylates the histone-like protein, MuLV p10; this appears to be correlated with release of the ribonucleoprotein from stable mature cores. Such a phosphorylation would most likely be related to uncoating of the virus particle after it has entered the cytoplasm of the infected mouse cell. (2 Refs)

44. EXPRESSION OF FELINE SARCOMA VIRUS 'GAG-FES' IN CULTIVATED CAT TUMOR CELLS (MEETING ABSTRACT).

Chen A, Kelliher M, De Noronha F, Essex M
Department of Microbiology, Harvard University School of Public Health, Boston, MA, 02115
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

A transformation-specific polyprotein designated 'gag-fes' has been described in mink or rat cells that are transformed with Snyder-Theilen (ST) and/or Gardner-Arnstein (GA) strains of feline sarcoma virus (FeSV). By inoculating cats with autologous cells that have been transformed with FeSV, we demonstrated that the natural feline host was capable of mounting a humoral immune response to the fes component. Antiserum specific to the fes component, obtained by adsorption with virus proteins, also reacts positively with feline oncornavirus associated cell membrane antigen-containing feline lymphoma cells by membrane immunofluorescence, suggesting the presence of a shared antigenic determinant. Expression of 'gag-fes' proteins was found to be coordinated with malignant phenotype in in vitro transformed cat cells as it is known to be in mink cells. Both producer and non-producer cells transformed with FeSV expressed this protein. To determine if the 'gag-x' class of proteins in general, and particularly 'gag-fes', are also expressed in malignant tumor cells that arise in vivo, biopsied tumor tissue was examined following short-term explanation and/or cultivation. Cultivated fibrosarcoma cells from 4 of 4 cats inoculated with ST-FeSV and 5 of 5 cats inoculated with GA-FeSV expressed the respective 'gag-fes' protein. This antigen was present both immediately after cultivation and also retained after at least 20 subcultivations. The same 'gag-fes' proteins were found in cultivated tumor cells from cats with FeSV-induced melanomas. However, the 'gag-fes' protein was not found in tissues from any of the 5 spontaneous tumors of comparable tissues that occurred in virus-free cats. (no Refs)

45. DETECTION OF A FACTOR IN THE PLASMA OF BOVINE LEUKEMIA VIRUS INFECTED CATTLE THAT BLOCKS THE EXPRESSION OF THE VIRAL GENOME IN INFECTED LYMPHOCYTES (MEETING ABSTRACT).

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New Bolton Center, University of Pennsylvania, Philadelphia, PA
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

Bovine Leukemia Virus (BLV) infected lymphocytes do not produce virus particles, viral antigens or viral RNA unless they are cultured in vitro for a few hr. To determine whether the expression of BLV genome in these cells is blocked by a soluble factor we have applied the competitive radioimmunoassay to examine the presence of the major internal virion antigen (p25) in BLV infected bovine lymphocytes before and after 24 hr of cultivation in the presence of plasma or serum of various origin. The plasma but not the serum of virtually all BLV-infected cattle blocked the expression of BLV p25. In contrast, no blocking was observed with plasma or serum from BLV-free cattle or from cattle infected with other common bovine viruses. The expression of BLV p25 could also be blocked by adding plasma from BLV-infected cattle to BLV-producing lymphocyte cultures. Removal of the blocking plasma from BLV infected lymphocyte culture was followed by the expression of BLV p25. The absence of the blocking factor in serum of BLV-infected cattle indicates that it is not BLV antibody. The factor is sensitive to protease, but not to DNAse or RNAse. It is dialyzable and is inactivated by heating at 56C for 10 min. (no Refs)

GENETICS

46. GENETIC STUDY OF LYMPHOMA INDUCTION BY AKR MINK CELL FOCUS-INDUCING VIRUS IN AKR X NFS CROSSES.

Cloyd MW, Hartley JW, Rowe WP
Lab. Persistent Viral Diseases, NIH, Rocky Mountain Laboratories, Hamilton, MT, 59840
J Exp Med; 154(2):450-458 1981

AKR mice were crossed with NFS mice. Susceptibility to lymphoma induction by AKR-247 mink cell focus-inducing (MCF) virus was measured in AKR and NFS mice, F1, F2, and various backcrosses. AKR mice, inoculated as babys or weanlings, were totally susceptible. NFS mice were totally resistant. F1 mice were completely susceptible if inoculated as babys, and partially susceptible if inoculated as weanlings. Among backcrosses, 52% were susceptible. Among F2 mice, 75% were susceptible. Virological assays indicated that AKR-247 MCF viruses were replicated only in mice containing the endogenous AKR ecotropic virus. If one virus was absent, the other was also absent. Among virus-positive mice 37% were resistant to MCF lymphomagenesis. Apparently an additional gene was involved in the development of the lymphoma. Mice with both virus-inducing loci seemed to be more susceptible than those with only one. The presence of ecotropic virus involved the generation of MCF viruses and established permissiveness for their growth. (20 Refs)

47. THE P21 SRC GENES OF HARVEY AND KIRSTEN SARCOMA VIRUSES ORIGINATE FROM DIVERGENT MEMBERS OF A FAMILY OF NORMAL VERTEBRATE GENES.

Ellis RW, DeFeo D, Shih TY, Gonda MA, Young HA, Tsuchida N, Lowy DR, Scolnick EM
Lab. Tumor Virus Genetics, NCI, Bethesda, MD, 20205
Nature; 292(5823):506-511 1981

The Harvey and Kirsten strains of murine sarcoma virus encode enzymatically and serologically related p21 src proteins which are required for virally mediated cellular transformation. The genes in each virus encoding p21 show such extensive divergence from each other that cloned probes from these genes detect distinct sets of cellular genes in the DNA from several vertebrate species. These data suggest that cellular p21 sarc genes constitute a divergent family of vertebrate genes that can regulate the growth of cells. (Author abstract) (39 Refs)

48. MAPPING OF THE FV-4 MOUSE GENE CONTROLLING RESISTANCE TO MURINE LEUKEMIA VIRUSES.

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Dept. Genetics, Inst. Medical Science, Univ. Tokyo, 4-6-1 Shirokanedai Minatoku, Tokyo 108, Japan
Int J Cancer; 28(2):237-240 1981

Fv-4, a gene controlling susceptibility to ecotropic murine leukemia viruses, was linked to both Pre-I (prealbumin) and Igh-I (immunoglobulin heavy-chain constant region) loci on chromosome 12 in mice. The gene order was Fv-4-Pre-I - Igh-I, and the estimated frequency of recombination between Fv-4 and Pre-I was about 20%. (Author abstract) (29 Refs)

49. GENETIC INTERACTIONS IN THE INDUCTION OF ECOTROPIC MURINE LEUKEMIA VIRUS (MEETING ABSTRACT).

McCubrey J, Risser R
McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, WI, 53706
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 294 pp., 1981.

The frequency of cells that produce ecotropic murine leukemia virus (MuLV) after induction in vitro with halogenated pyrimidines has been investigated in several low leukemic strains of mice. Very few induced embryo cells of the strains BALB or C57BL/6 produce MuLV; this low frequency is increased 10-50 fold in (BALB x B6) F1 hybrid mice. Data from backcrosses of the F1 hybrid to either parent and (BALB x B6) F2 mice indicate that the phenotype of enhanced MuLV production is a consequence of the interaction of two unlinked loci, dominant (+/+) alleles of which are carried by either parent. Preliminary data indicate that the complementing gene carried by BALB/c mice not on the same chromosome as Cv-1, the single ecotropic provirus of BALB/c mice. Other data suggest that the complementing locus carried by B6 mice may well be Bv-1, the single ecotropic provirus of C57BL mice. Examination of hybrids of other strains with BALB and B6 led us to conclude that A/J and C3H mice carry +/+ alleles at Inc-1 whereas NFS, SWR, DBA/2, and 129 mice carry -/- alleles at both complementing loci, although DBA/2 mice are known to encode a co mplete ecotropic MuLV provirus. The identification of these genetic loci which specifically interact to enhance MuLV production on induction suggests that additional intracellular mechanisms exist for the propagation and control of MuLV expression. (no Refs)

50. MUTANTS OF ROUS SARCOMA VIRUS WHICH AFFECT TRANSFORMED CELL MORPHOLOGY AND EXHIBIT ALTERED PP60SRC MOLECULES (MEETING ABSTRACT).

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RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

Four Rous sarcoma virus strain SR-A mutants (ST529, W0101, W0201, W0401), arising from stocks independently mutagenized with one of four different mutagens, cause an elongated, or fusiform (morph f) transformed cell morphology in chicken embryo fibroblasts at 37C. The 'pp60src' species isolated from cells transformed by these mutants possess protein kinase activity, as measured by phosphorylation of IgG heavy chains. However, the mutant 'pp60src' species exhibit an apparent mol wt of 54-55K on sodium dodecyl sulfate (SDS) polyacrylamide gels, in contrast to the 59-60K Mr pp60src species isolated from wt SR-A transformed cells, using the same extraction conditions. This difference was observed both with extraction buffers containing SDS, sodium deoxycholate and NP40, as well as with buffers not containing SDS and sodium deoxycholate. Partial digestion experiments utilizing Staphylococcus aureus V8 protease indicate that all four mutant 54-55K src species are lacking peptides present in the N-terminal half region of wt pp60src molecules. These results suggest that a common, or similar, structural defect in the mutant 54-55K src species is intimately related to, and perhaps the cause of, the morph f phenotype exhibited by cells transformed by these particular mutants. (1 Ref)

IMMUNOLOGICAL STUDIES

51. NATURAL ANTIBODIES TO THE HUMAN T CELL LYMPHOMA VIRUS IN PATIENTS WITH CUTANEOUS T CELL LYMPHOMA.

Posner LE, Robert-Guroff M, Kalyanaraman VS, Poiesz BJ, Ruscetti FW, Fossieck B, Bunn PA, Minna JD, Gallo RC
Lab. Tumor Cell Biology, NIH, Bethesda, MD, 20205
J Exp Med; 154(2):333-346 1981

Serum samples were obtained from patients with cutaneous T cell lymphoma (CTCL) and leukemia, and from 55 normal random donors. Retroviruses HTLV-CR (grown in HUT 102 cells) and HTLV-MB, isolated from patients CR and MB, respectively, were used, along with several other retroviruses. The sera were screened for the presence of natural antibody to HTLV-CR, using a solid-phase radioimmunoassay. Sera from patient CR and one other patient reacted specifically with proteins of HTLV-CR. CR serum also reacted with HTLV-MB proteins. Solid-phase immunocompetition and competition radioimmunoprecipitation assays demonstrated the specificity for HTLV-CR proteins. Patient CR antibodies were directed against viral core proteins with mol wt of 24,000 and 19,000, as shown by radioimmunoprecipitation analysis. Some reactivities to other animal retroviruses, including the baboon endogenous virus, simian sarcoma virus, feline leukemia virus, and gibbon ape leukemia virus, were demonstrated. These reactivities apparently were not virus-specific, but related to cellular antigen contamination of viral preparations or to antigens in fetal calf serum. The results indicate for the first time a specific antibody reaction to a retrovirus in humans. (38 Refs)

52. REACTIVITY OF ANTISERA TO ANTIGENS OF C-TYPE VIRUSES WITH LEUCOCYTES FROM PATIENTS WITH ACUTE LEUKAEMIA.

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Pathology; 13(2):289-298 1981

A number of previous studies have suggested that certain C-type viruses from non-human primates are associated with acute leukemia in humans. The present study sought to examine this association further by detection of antigens related to these viruses on the surface of acute leukemia cells. Antisera against the whole viruses or the major internal protein of simian sarcoma, endogenous baboon and Rauscher viruses were tested against mononuclear cells from patients with acute leukemia at various stages of their disease in 51Cr release WBC dependent cytotoxic assays. A high proportion of the patients had antigens related to these viruses detectable on their blood WBC at some stage in their disease whereas with one exception blood WBC from non-leukemic subjects did not. The expression of these antigens did not show a close relation to the number of blast cells in blood detected on morphological grounds. Antigens related to the non-human primate viruses were detected on mononuclear cells from bone marrow samples of several non-leukemic patients which indicated they were not specifically associated with leukemia. Antigens related to the Rauscher virus were detected on cells of practically all bone marrow samples tested. These results suggest that assays to detect these antigens would be of limited usefulness to monitor disease activity in patients with acute leukemia. Their expression on blood WBC however appeared strongly associated with acute leukemia and further studies to assess the prognostic and epidemiological significance of detection of these antigens appears warranted. (Author abstract) (16 Refs)

53. IMMUNOTHERAPY OF MURINE LEUKEMIA. V. PROTECTION AGAINST FRIEND LEUKEMIA VIRUS-INDUCED IMMUNE COMPLEX GLOMERULONEPHRITIS BY PASSIVE SERUM THERAPY.

Sanfilippo F, Genovesi EV, Collins JJ
Duke Univ. Medical Center, P.O. Box 3712, Durham, NC, 27710
JNCI; 67(3):703-717 1981

The development of immune complex glomerulonephritis in DBA/2 mice infected with Friend murine leukemia virus (F-MuLV) was compared with that in mice protected against virus-induced disease by administration of chimpanzee anti-F-MuLV antiserum (CaF-MuLV). Morphologic analysis of glomeruli from viremic (infected) normal chimpanzee serum-treated animals revealed significant renal disease within 2 wk following virus inoculation, with glomerular immune complex deposits and C-type viral particles seen by electron microscopy. Localization of F-MuLV envelope and core antigens (gp71 and p30, respectively) was also detected by immunofluorescence, as was murine IgG and C3. However, age-matched DBA/2 mice treated with CaF-MuLV antiserum alone or following F-MuLV inoculation showed no evidence of systemic disease and neither localization of F-MuLV antigens nor detectable virus particles. These data indicate that in addition to erythroleukemia, F-MuLV infection results in severe immune complex glomerulonephritis and that passive immunotherapy can protect susceptible mice from both aspects of viral pathogenesis. (Author abstract) (30 Refs)

54. GRAFT-VS-LEUKEMIA AND MODERATION OF GRAFT-VS-HOST REACTION IN TRANSPLANTATION THERAPY OF VIRAL LEUKEMIA.

OKunewick JP, Meredith RF, Raikow RB, Brozovich BJ, Magliere K
Cancer Res. Lab., Allegheay General Hosp., Pittsburgh, PA, 15212
Exp Hematol; 9(7):754-765 1981

In transplantation studies of Rauscher leukemic SJL/J mice longer median survival times (MST) were obtained with spleen cells from syngeneic donors than with marrow. These could be further extended by immunization of the donors to Rauscher virus (RLV) and Rauscher leukemia cells. This suggests that spleen cells exert a greater graft-vs-leukemia effect than marrow. Nevertheless, with syngeneic cells all recipients eventually died of leukemia relapse. In contrast, the use of RLV-resistant C57BL/10J allogeneic marrow cells resulted in a substantial number of long-term survivors and a low incidence of GvH disease, while the use of pure allogeneic spleen cells resulted in early and fatal GvH response in all recipients. To determine if allogeneic spleen cells might have any demonstrably beneficial effect on survival of leukemic mice various small quantities of C57BL/10J spleen cells were mixed with marrow from the same donors and engrafted into normal and leukemic SJL/J recipients. Among the normal mice MST decreased as a function of spleen cell concentration. However, with the leukemics the use of 2.5 or 5% spleen cells resulted in later deaths than that found when leukemic mice were given only marrow. Also, for all allogeneic spleen/marrow mixtures tested, survival of leukemic recipients exceeded that of normal recipients given the same cell mixtures. These data suggest a possible beneficial effect of small amounts of allogeneic spleen cells in transplantation therapy for leukemia, and a possible competitive interaction of anti-host and anti-leukemic activities of the transplanted cells leading to a moderation of the GvH response. (Author abstract) (30 Refs)

55. NATURAL KILLER CELLS KILL TUMOUR CELLS AT A GIVEN STAGE OF CELL DIFFERENTIATION.

Gidlund M, Orn A, Pattengale PK, Jansson M, Wigzell H, Nilsson K
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Nature (Lond); 292(5826):848-850 1981

The effect of differentiation-inducing agents on the natural killer (NK)-cell susceptibility of three tumor cell lines was studied: K-562, a human erythroleukemia cell line; U-937, a human histiocytic lymphoma cell line; and GM-86, a murine Friend virus-induced leukemia originating in DBA/2J mice. The cells were tested for NK-sensitivity in a 57Cr-release assay, with Ficoll-Isopaque-isolated human peripheral blood cells used as effector cells for the human target cells and mouse spleen cells used as effector cells for the GM-86 target cells. The NK-cell sensitivity of K-562 cells decreased after exposure to sodium butyrate or hemin, and this decrease was correlated in time with an increase in erythroid differentiation markers. Treatment of U-937 cells with 12-O-tetradecanoylphorbol-13-acetate or supernatants from mixed lymphocyte cultures induced the appearance of cells with a macrophage-like appearance and resulted in a concomitant reduction in NK-cell sensitivity. Following hexametabisacetamide treatment, the GM-86 cells acquired the capacity of globin production but showed decreased NK-cell susceptibility. These results supported the hypothesis that susceptibility to NK cells may vary according to the differentiation stage of the tumor target cell. (24 Refs)

56. QUANTITATION AND CLONAL ISOLATION OF CYTOLYTIC T LYMPHOCYTE PRECURSORS SELECTIVELY INFILTRATING MURINE SARCOMA VIRUS-INDUCED TUMORS.

Brunner KT, MacDonald HR, Cerottini JC

Dept. Immunology, Swiss Inst. for Experimental Cancer Res., 1066 Epalinges, Switzerland

J Exp Med; 154(2):362-373 1981

Moloney sarcoma virus (MSV) tumors were induced in inbred female C57BL/6 mice by injecting a cell-free homogenate of MSV/Moloney leukemia virus (MSV/MoLV) complex. A MoLV-induced lymphoma, MBL-2 (H-2b), was maintained by passage in C57BL/6 mice. Two chemically-induced tumors, P815 (H-2d) and EL4 (H-2b), and a MoLV-induced lymphoma, LSTRA (H-2d), were maintained in vitro. Ten days after injection with MSV/MoLV complex, lymphoid cell pools were prepared from the spleens, blood, and tumors of the injected mice. Cytolytic T lymphocytes (CTL) and their precursors (CTL-P) were quantified, using a mixed leukocyte-tumor cell microculture method. Tumor-derived cell populations were found to contain 7-8 times as many tumor-specific CTL-P as populations from spleens or peripheral WBC. CTL-P frequency in tumor tissue was explained by the selective accumulation of a T cell subpopulation bearing CTL-P surface markers. Measured according to the content of Lyt-2+ cells, CTL-P frequencies were 1/9 in tumor-infiltrating cells, 1/45 in spleen cells, and 1/41 in peripheral blood lymphocytes. This indicated a selective accumulation of CTL-P in the tumors. Highly cytolytic cells from the tumor-derived populations were cultured. Five out of six populations showed high cytolytic activity. These five populations showed specificity for the MoLV-derived syngeneic MBL-2 targets, but not for MoLV-derived allogeneic or allogeneic target cells unrelated to MoLV. (25 Refs)

57. IMMUNE RESPONSIVENESS OF HRS/J MICE TO SYNGENEIC LYMPHOMA CELLS.

Johnson DA, Meier H

Jackson Lab., Bar Harbor, ME, 04609

J Immunol; 127(2):461-464 1981

HRS/J, hr/hr and hr/+ mice were evaluated and their ability to resist challenge with a syngeneic tumor, HTU, and for their ability to mount a protective immune response when immunized in vivo with inactivated HTU cells previous to challenge with viable tumors. The heterozygous (hr/+) mice responded more strongly than the homozygous (hr/hr) mice. This response was characterized by the presence of an enhanced ability of spleen cells from immunized mice to form blasts in vitro when incubated with purified murine leukemia viruses (MuLV). We conclude that the in vivo response of HRS/J mice against this tumor is directed, in part, against MuLV antigens expressed on the tumor cells and that the relatively weak response of hr/hr spleen cells to these antigens may be mechanistically linked to their tumor susceptibility. (Author abstract) (17 Refs)

58. FELINE LEUKEMIA - UNIQUE AND CROSS-REACTING ANTIGENS ON INDIVIDUAL VIRUS-PRODUCING TUMORS IDENTIFIED BY COMPLEMENT-DEPENDENT ANTIBODY.

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Int J Cancer; 28(2):209-217 1981

Following exposure to feline leukemia virus (FeLV), cats that resist leukemia produce complement dependent antibodies (CDA) which lyse leukemia cells in the presence of cat complement. The CDA activity has been shown to be directed to feline oncornavirus-associated cell membrane antigen (FOCMA) found on the surface of most feline leukemias. Despite the retrovirus etiology of feline leukemia, and the ubiquity of FOCMA expression by individual tumors, we found that CDA activity did not cross-react when five feline leukemia lines were compared (FL74, F422, 3272, 3281, and 79-14940). Profiles for CDA mediated lysis of the leukemia target lines were determined for sera from 149 FeLV exposed cats, and animals were identified whose sera would selectively lyse almost any possible combination of tumors from one to five lines tested. Cross absorption and cold target inhibition studies were performed on selected sera, and a spectrum of different antigens was identified which included both individual determinants and antigens shared by some of the tumor lines. Leukemias FL74 and F422 carried a cross-reactive determinant which was distinct from a second antigen shared by 3272 and 3281; lines F422, 3272 and 3281 each also carried a unique antigen. Leukemia 79-14940 did not cross-react with other target tumor lines. Targets of CDA mediated lysis on leukemia cells may be associated with normal feline cell surface antigens, because CDA titers were sometimes reduced after serum absorption with normal cat spleen cells. The relevance of multiple FOCMA determinants is discussed in terms of tumor escape from immunity. (Author abstract) (30 Refs)

59. EVALUATION OF THE PARAMETERS OF THE ELISA PROCEDURE FOR FELINE TYPE C RETROVIRAL ANTIGENS: ASSAY OF FELV ANTIGENS IN CHRONICALLY INFECTED OR NONPRODUCER TRANSFORMED CELLS.

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Intervirology; 15(1):1-9 1981

The successful application of an improved enzyme-linked immunosorbent assay (ELISA) to the specific detection and quantitation of feline leukemia virus (FeLV) is presented. The methods described can detect FeLV antigens at the picog/ml level using a fluorometric assay for peroxidase-linked antibody. The use of a fluorogenic substrate resulted in at least a 9-fold increase in sensitivity of the peroxidase assay. FeLV antigens could be specifically detected in chronically infected cells as well as in feline sarcoma virus-transformed nonproducer mink cells which only partially express viral proteins. (Author abstract) (26 Refs)

60. IMMUNOLOGIC ASPECTS OF CANCER.

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Hosp Pract; 16(7):85-88,90,93-95 1981

Current research in the field of tumor immunology is reviewed with special emphasis on the identification of tumor-specific antigens. In vitro techniques demonstrated that tumors and leukemias induced by oncornaviruses express the transplantation antigens. Tumors induced by chemical antigens or oncogenic viruses were found to vary in their ability to render mice immune to subsequent challenge with the same tumor. Human tumor-specific antigens defined by heterologous sera were shown to be differentiation antigens. An autologous typing of greater than 200 melanoma patients revealed three classes of surface antigens, ie antigens restricted to the autologous tumor and not detectable on autologous normal cells; shared tumor antigens, expressed by autologous as well as by some allogeneic tumors of similar or different origin; and antigens widely distributed on autologous, allogeneic, and xenogeneic normal and malignant cells . Development of serologic typing systems for defining cell surface antigens of melanoma and other cancers provided the basis for assaying a number of different melanoma vaccines. (5 Refs)

61. CELL MEDIATED RESPONSES TO CERTAIN BREAST CANCER ASSOCIATED ANTIGENS (MEETING ABSTRACT).

Bernhard MI, Pace RC, Wanebo HJ, Pace RC

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4th Annual San Antonio Breast Cancer Symposium, Nov 6-7, 1981, San Antonio, Texas Cancer Therapy and Research Center of South Texas; 1981

Breast cancer patients have been shown to have significant cell mediated immune (CMI) responses to certain putative cancer associated antigens in comparison to patients with benign breast disease and normal controls. These antigens include the Murine Mammary Tumor Virus (MTV) obtained from RIII strain mouse milk, a human breast cancer derived cell line (MCF-7), and the T antigen, a precursor to the MN blood group. We have sought to measure CMI responses to these antigens in a broader group of cancer patients to define the range and selectivity (if any) of these responses. Direct WBC migration inhibition tests were performed on blood samples from 66 normal controls, 16 benign breast disease patients, 69 breast cancer patients, 21 patients with epidermoid cancer of the head and neck, 33 colorectal cancer patients, and 33 melanoma patients. When patients were tested repeatedly on different dates, each test was considered a separate test. Paired tests were run simultaneously with saline extracts of (MCF-7) (20 ug/ml), frozen and thawed, MTV (2.5 ug/ml), T antigens (20 ug/ml), a common bacterial antigen Staph-phage Lysate (SPL), the mitogen Con A, and saline extracts of paired normal and breast cancer tissues. Regression analysis revealed that all cancer patients tested demonstrated highly significant correlation in their responses to MTV, MCF-7, and the T antigen (P less than 0.01), but not to SPL. Controls showed no correlated responses to MTV, MCF-7, or the T antigen. These data suggest that these antigens either share common antigenic determinants or are similar enough to cross-react in this assay. The demonstration of these responses in cancer patients of non-breast cancer origin raises questions about the reported restriction of these antigens to breast cancer patients. (no Refs)

62. APPROACHES TOWARD IMMUNOTHERAPY OF 'NON-ANTIGENIC' TUMORS (MEETING ABSTRACT).

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RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 294 pp., 1981.

Our laboratory has been successful in the immunological management of several different tumors associated with type-C retroviruses by utilizing the virus antigens as targets for immune attack. There is a large body of virus negative tumors, however, which are non-antigenic and refractory to immunological manipulations. The current study deals with our initial attempts at rendering a virus negative methylcholanthrene-induced, transplantable sarcoma susceptible to immunotherapy after infection with FLV. Six courses of treatment with 0.5 ml of a high titered heterologous goat anti-FLV gp71 antiserum administered IP was found to have a profound effect on the outgrowth of the infected tumor (4% with tumor) when compared with normal goat serum (80% with tumor). The specificity of treatment was determined by conducting the therapy on the uninfected counterpart. In this case, there was no difference in tumor outgrowth between goat anti-gp71 treated, normal goat serum treated, or untreated groups. That the effect seen with the goat anti-gp71 is actual therapy is evident by the fact that successful treatment could be initiated at times when demonstrable tumor nodules were present. Thus, converting lowly antigenic virus negative tumors to highly antigenic virus positive tumors is a feasible approach toward rendering them susceptible to immunotherapy with anti-viral immune reagents. (no Refs)

63. INHIBITION OF T CELL BLASTOGENESIS OF C57BL/6 REGRESSOR MICE TO MOLONEY LEUKEMIA VIRUS GLYCOPROTEIN GP70 BY ANTI-GP70 MONOCLONAL ANTIBODY (MEETING ABSTRACT).

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Immunobiol; 159(1/2):34 1981

The antigenic specificities of the humoral and cellular immune responses of C57BL/6 mice undergoing regression of tumors induced by the complex Moloney leukemia virus (MoLV)/Moloney sarcoma virus (MSV) have been recently elucidated in our laboratory. It was found that MoLV/MSV regressor mice produced antibodies directed primarily against MoLV envelope proteins p15(E) and gp70, and, to a lesser extent, against the internal protein p12. Furthermore, it was shown that splenic T cells derived from MoLV/MSV regressor mice could undergo in vitro blastogenesis when stimulated with either MoLV gp70 or p12. Only one of five hybridoma antibodies, 2A1, having specificity for MoLV gp70 was able to significantly reduce MoLV/MSV immune T cell proliferative response to MoLV gp70. This inhibition was specific for gp70, as demonstrated by the inability of anti-p12 monoclonal antibody to block T cell blastogenesis. Since only a max of 80% inhibition of blastogenic response to gp70 was obtained with antibody 2A1, it is suggested that more than one antigenic determinant on the gp70 molecule is responsible for eliciting in vitro T cell proliferation. In studying the mechanism of blastogenesis, it was observed that supernatants from cultures of MoLV/MSV immune T cells incubated with gp 70 contained factor(s) capable of stimulating normal T cells to proliferate (subsequently referred to as blast factors). A likely prediction is that antigen-reactive T cells recognize gp70 and release blast factors which can then induce the proliferation of another T cell subset. The latter step is therefore antigen-independent. It was found that 2A1 antibody could indeed block the capacity of antigen-reactive T cells to produce blast factors, but was totally ineffective in reducing the proliferation of normal T cells in the presence of blast factors prepared in the absence of inhibitor. (no Refs)

64. MONCOLONAL ANTI-GP70 ANTIBODIES CAUSE IN VIVO REDUCTION OF FRIEND VIRUS INFECTIOUS CENTERS IN LEUKEMIC SPLEENS (MEETING ABSTRACT).

Chesebro B, Britt WJ
Laboratory of Persistent Viral Diseases, Rocky Moutain Laboratories, Hamilton, MT
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 294 pp., 1981.

Monoclonal antibodies which treated with gp70, p15 and p15E proteins of Friend virus (FV) were obtained from hybridomas derived from spleen cells of mice recovering from Friend virus-induced erythroleukemia. Two antibodies appeared to have the Friend-Moloney-Rauscher pattern of specificity. One of these was specific for gp70 and the other for p15. Seven other anti-gp70 antibodies and 1 anti-p15 were restricted in reactivity to Friend and Rauscher viruses, and some Friend-MCF viruses. Two to four days after inoculation of monoclonal antibody, three different IgG2a anti-gp70 antibodies caused a 10-to 1000-fold reduction in the number of spleen cells scoring as F-murine leukemia virus infectious centers without reducing the number of leukemic cells containing cytoplasmic viral antigens. Monoclonal IgG2a or IgG2b anti-p15 and IgM anti-gp70 antibodies did not cause this effect in spite of the fact that these antibodies could lyse FV leukemia cells or FV-infected cells in vitro in the presence of complement. One possible mechanism for the reduction of infectious centers by anti-gp70 antibodies was decreased release of infectious virus from cells as a result of antibody-induced modulation of cell surface gp70 molecules. However, the short time interval between exposure to antibody and observation of decreased infectious centers would appear to make this mechanism less likely. These results appeared to mimic the effect of the Rfv-3 gene seen in (B10.A X A) F1 mice 30-60 days after FV inoculation, where virus release was markedly reduced in spite of continued massive splenomegaly. (no Refs)

65. MONOCLONAL ANTIBODIES TO SFFV-ENCODED GP52 CROSS-REACT WITH RECOMBINANT MCF AND XENOTROPIC VIRUSES (MEETING ABSTRACT).

Wolff L, Ruscetti S
Laboratory of Tumor Virus Genetics, National Cancer Institute, Bethesda, MD
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

The spleen focus-forming virus (SFFV) encodes, a 52,000 dalton glycoprotein that shares antigenic determinants with the gp70 of a variety of recombinant MCF viruses. In order to obtain immunological reagents reactive with defined determinants on SFFV gp52, hybridoma cell lines secreting monoclonal antibodies to gp52 were prepared by fusing SP-2 mouse myeloma cells with lymphocytes from OM rats immunized with SFFV/normal rat kidney nonproducer cells or semi-purified gp52. Hybrid cells producing IgG or IgM antibodies reactive with Friend MCF virus were detected by a radioimmune binding assay employing whole, disrupted virus. From 3 fusions, approx 75 hybrid lines were chosen for cloning, and 13 were stable and formally cloned twice. Antibody from several of these reacted with Friend (F) MCF and not F-Murine leukemia virus (MuLV) and were thus good candidates for monoclonals to SFFV gp52. One of these has been extensively characterized using immune precipitation and polyacrylamide gel electrophoresis. This antibody is specific for a determinant on SFFV-encoded gp52 and is cross-reactive with the gp70's of a number of MCF viruses, including AKR MCF 247 and Moloney MCF 83. The monoclonal also recognizes a determinant on the gp70's from a variety of xenotropic and amphotropic virus isolates. However, it fails to react with the gp70's of any ecotropic viruses tested, with the exception of one stock of ecotropic Moloney MuLV. It also fails to react with the gp70 encoded by the feline leukemia virus. (no Refs)

66. IN VITRO GROWN T CELL LYMPHOMAS THAT EXPRESS CYTOTOXIC ALLOREACTIVITY (MEETING ABSTRACT).

Proffitt MR, DeLamotte C
Cleveland Clinic Foundation, Cleveland, OH
Immunobiol; 159(1/2):150 1981

We have been studying T cell lymphomas, derived in our laboratory, which may be the malignant counterparts of clones of normal cytotoxic T cells. These lymphomas were derived from C3H/HeJ mice infected as newborns with Moloney murine leukemia virus. The cells of one of these in vitro grown lymphomas (C3HMT1893) exhibit rather specific cytotoxic reactivity when assayed on murine fibroblasts. Grown conventionally (ie, not stimulated with exogenous interleukin 2 and not grown or assayed in the presence of ligands), C3HMT1893 cells preferentially kill BALB/c target fibroblasts; they do not kill identically derived BALB/c targets infected with MuLV-M. Moreover, they do not kill normal murine fibroblasts of several other allotypes, Con-A-stimulated murine lymphoblasts, or xenogenic target cells. Two clones derived from the parent tumor behave similarly. A different T cell lymphoma (C3HMT1820) displays a different pattern of cytotoxicity on the same spectrum of target cells. The virus itself does not seem to be directly responsible for these phenomena since C3HMT1893 cells produce little detectable infectious MuLV, whereas C3HMT18 20 cells actively produce the virus. (no Refs)

67. H-2 CONTROL OF THE CYTOTOXIC T CELL RESPONSE AGAINST MOLONEY (ABELSON) LEUKEMIA VIRUS (MEETING ABSTRACT).

Stukart MJ, Vos A, Melief CJ
University of Amsterdam, Amsterdam, The Netherlands
Immunobiol; 159(1/2):193 1981

The secondary cytotoxic T cell (CTL) response against Moloney (Abelson) leukemia virus [M(A)-MuLV] could be efficiently measured using syngeneic M(A)-MuLV-infected lymphoblasts as stimulator cells for secondary in vitro restimulation and as target cells for virus-specific destruction. Only lymphoblasts obtained after stimulation of normal spleen cells with the B cell mitogen lipopolysaccharide (LPS) and infected with the virus were excellent targets for virus-specific CTL, whereas M(A)-MuLV-infected concanavalin A stimulated T cell blasts were not. This method was used to measure secondary CTL responses against M(A)-MuLV in C57BL mice of a variety of H-2 haplotypes. In C57BL/6 (KbDb) mice strong virus-specific CTL reactions were seen against syngeneic targets cells, intermediate reactions occurred in 2R (KkDb) and 4R (KkDb) mice and weak reactions in 5R (KbDd) mice. In addition B6 (KbDb) CTL effectively lysed 4R (D compatible) but not 5R (K compatible) cells. Thus in B6 mice CTL responsiveness is mainly associated with Db and Db appears to be the predominant regulatory H-2 element determining positive CTL responsiveness. This conclusion was confirmed by experiments with two mutants of the Db locus of C57BL/6: the bm13 and bm14 mutants. Both mutations profoundly affected the restriction specificity of H-2D restricted CTL, because 4R effector cells did not lyse bm13 (KbDbm13) and bm14 (KbDbm14) target cells and because bm13 effector cells did not lyse virus-infected 4R target cells. The bm14 mutation was associated with a complete loss of the capacity to mount a CTL response to M(A)-MuLV. The bm13 Db locus led to a strongly increased capacity to mount a Kb associated CTL response, because 5R (KbDd) virus-infected target cells were lysed much better by bm13 (KbDbm13) CTL than by B6 (KbDb) CTL. The strong Kb restricted component in the CTL response of bm13 effector cells against 5R target cells is further demonstrated by the obervation that they did not lyse Kb mutant bm1 (kbm1Db) virus-infected target cells. (no Refs)

68. HELPER T CELL RESPONSE AGAINST MOLONEY LEUKEMIA VIRUS IN MICE (MEETING ABSTRACT).

Debre P, Boyer B, Levy JP
No affiliation given
Immunobiol; 159(1/2):34 1981

In previous reports we demonstrated that the level of viremia and the appearance of leukemias in mice inoculated with Moloney leukemia virus (MLV) were under H-2 and non H-2 genetic control. Three genes within the major histocompatibility complex controlled the level of circulating virus Two of them called Rmv1 and Rmv2 appear to be located in the I region, respectively in the IA and IC-S or G region. The third gene, Rmv3 was mapped to the D end of the complex in D or T region. Further studies demonstrated that Rmv1, Rmv2 and Rmv3 function as immune response (Ir) genes regulating the level of antiviral antibodies. To study more precisely the helper T cell function, we performed experiments in culturing anti MLV spleens or lymph nodes with DNP-MLV. This system allowed us to characterize 1) the timing and specificity of antiviral immune response in mice inoculated by murine sarcome virus (MSV) or inactivated MLV, 2) the phenotype and genetic control of specific helper T cells, 3) the relationship of helper function with other components of immune response in MSV infected mice. (no Refs)

69. ABELSON VIRUS TRANSFORMANTS USUALLY HAVE REARRANGED HEAVY CHAIN GENES BUT NOT LIGHT CHAIN GENES (MEETING ABSTRACT).

Alt F, Rosenberg N, Thomas E, Lewis S, Baltimore D
Massachusetts Institute of Technology, Cambridge, MA, 02139
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 294 pp., 1981.

Infection of bone marrow or fetal liver cultures with Abelson murine leukemia virus (A-MuLV) transforms a small fraction of the cells into clonal, continuous cell lines. Approx 60% of such cell lines from marrow or 18-19 day liver express immunoglobulin (Ig) u heavy chains, but no light chains indicating that the cells are related to the pre-B-lymphocyte. The majority of the remainder as well as a 90% of transformants from 13 day fetal liver produce no detectable Ig chains. All of the lines, whether Ig-containing or null, had DNA rearrangements at the JH regions of both chromosomes indicating that the rearrangement process that generates a functional u gene had been active in these cells. A variety of control cells, including T cell lines, had no such rearrangement. None of the lines, except for rare light chain producers, had detectable rearrangements at either their kappa or lambda light chain loci. Ig producers had u messenger RNA species for both the secreted and membrane forms of u protein but the null cells had a characteristic set of cytoplasmic Cu-containing RNAs that did not encode any detectable protein and were aberrant in structure. Thus the u genes in all lines were transcriptionally active. These data show that in vitro, A-MuLV transforms only cells with hallmarks of the B-lymphoid lineage but that the resulting clones have a variety of molecular phenotypes. The mix of cells present at a specific time during development may be a determinant of the type of transformant that emerges. (no Refs)

70. VIRAL SRC GENE AND CELLULAR GENES INTERACTING IN THE EXPRESSION OF ROUS SARCOMA VIRUS (RSV)-INDUCED TRANSFORMATION AND TRANSPLANTATION CELL SURFACE ANTIGENS (MEETING ABSTRACT).

Prat M, Tarone G, Comoglio PM
Department of Histology, University of Trieste, School of Medicine, Trieste, Italy
Immunobiol; 159(1/2):189 1981

Avian and mammalian fibroblasts transformed by RSV express a serologically detectable virus-induced non-virion cell surface antigen (VCSA), whose expression is controlled by the transforming viral src gene. By inhibition experiments performed with cytotoxic antibodies and RSV-transformed cells of different animal species, it has been found that VCSA expression on transformed hamster fibroblasts is a complex of two antigenic specificities, one controlled by the viral genome and one controlled by the host cellular genome. By in-vivo immunization we have now found that RSV-transformed fibroblasts from different mouse strains share a virus-specific transplantation antigen. Immunoprecipitation tests with mono-specific antisera showed that the expression of this antigen does not correlate with the presence of intracellular viral proteins other than the src gene product pp60src. However, hyperimmunization of mice with hamster or quail fibroblasts transformed by RSV that express a high level of pp60src did not induce transplantation resistance. It is concluded that the expression of the serologically-defined VCSA and the transplantation antigen is the result of the interaction of pp60src with host cell gene product(s) rather than the simple exposure of pp60src at the outer cell surface. (no Refs)

OTHER RELATED STUDIES

71. A UNIFIED THEORY OF CARCINOGENESIS: ACTIVATION OF TRANSPOSABLE GENETIC ELEMENTS WITH ONCOGENIC POTENTIAL.

Renan MJ
Div. Radiation Oncology, Dept. Radiology, UCI Medical Center, 101 City Drive South, Orange, CA, 92668
Speculations Sci Technol; 4(1):7-20 1981

In developing a unified theory of carcinogenesis, several theories are critically examined, including the mutation model, viral etiologies, and two-stage and integrative theories. Aspects of viral genetics necessary for exposition of the author's model are discussed. A mechanism for the activation of endogenous sequences in vertebrates is proposed. A unified theory of carcinogenesis is presented. The model is then extended to include human neoplasia, and the 'transformon' theory is introduced. It is suggested that in mammalian and avian systems, endogenous genetic elements with transforming potential are activated when the survival of the host cell is threatened. These sequences may have evolved from recombinant events between retroviral genomes and normal cellular genes. It is proposed that human malignancy results from the activation of a transposable genetic element (or transposon) and the subsequent integration of this DNA segment into the genome of a suitable cell. The designation 'transformon' is suggested for the transposed sequence, which in the simplest model consists of a cellular oncogene, a gene coding for transposase, and a gene encoding a repressor protein. (161 Refs)

72. REVERSIBILITY OF THE TRANSFORMED AND NEOPLASTIC PHENOTYPE. I. PROGRESSIVE REVERSION OF THE PHENOTYPE OF X-RAY-TRANSFORMED C3H/10T1/2 CELLS UNDER PROLONGED TREATMENT WITH INTERFERON.

Brouty-Boye D, Gresser I
Institut de Recherches Scientifiques sur le Cancer, BP 8, 94802 Villejuif, France
Int J Cancer; 28(2):165-173 1981

X-ray transformed mouse C3H/10T1/2 cells were cultivated and passaged in the continuous presence of partially purified mouse interferon. This prolonged interferon treatment resulted in a stepwise progressive reversion of the transformed phenotype to the non-transformed phenotype. Thus interferon-treated cells displayed an epithelioid morphology, grew to a lower cell density, and were no longer tumorigenic. Reversion to the non-transformed phenotype was, however, stable only as long as interferon was continuously present in the culture medium. When interferon was removed, the cells 'back reverted' to the transformed phenotype. Our results suggest that interferon induced a reversion of the transformed phenotype in the entire cell population rather than a selection of an interferon resistant cell population. C-type viral particles and significant levels of reverse transcriptase were present in transformed cells, but neither were present in the parental 10T1/2 cells nor in interferon-treated cells. When interferon was removed from the culture medium, viral particles and reverse transcriptase activity were again detected. It is possible, therefore, that interferon induces reversion through its antiviral activity, or that it induces reversion by its effects on cell function and structure, independently of any antiviral effect. Inhibition of cell multiplication per se does not appear to be sufficient to induce reversion, since cycloheximide inhibited cell multiplication; however, even after ten passages, it did not affect tumorigenicity. Our results suggest the possibility that interferon may act in vivo not only by inhibiting tumor cell multiplication but also by inducing a reversion. Patients with some tumors may therefore benefit from long-term interferon treatment. (Author abstract) (24 Refs)

73. PLASMA MEMBRANE ENZYMES IN BALB/C LYMPHOMAS WITH EITHER T OR B CELL PROPERTIES. I. 5'-NUCLEOTIDASE.

Zachowski A, Simonin G, Aubry J, Pommier P, Singh SN, Potter M, Paraf A
ERA 802 CNRS, Laboratoire d'Immunologie Cellulaire EPHE, Station de Recherches de Virologie et d'Immunologie, INRA, 78850 Thiverval-Grignon, France
J Receptor Res; 2(1):97-118 1981

Membrane-bound 5'-nucleotidase activity was compared in crude extracts and plasma membrane fractions from murine plasmacytomas and thymomas. Clones of the tumor cells, judged representative of different steps in B and T cell differentiation according to surface antigen markers, were derived, respectively, from Abelson virus transformed lymphomas and IgM, IgA, and IgG producing plasmacytomas, and from thymomas with surface antigen markers characteristic of T suppressor and helper cells and of early T cell differentiation. Membrane fractions were obtained through cell lysis and purification. 5'-Nucleotidase activity was characterized by the following criteria: 1) optimal pH for enzyme activity (7.5-9.5 for B type lymphocytes and 5.5-6.5 for T type cells, except in Lut 13 membranes where it was 9.5); 2) specificity of 5'-AMP as a substrate at optimal pH (for all B cell categories and Lut 13, 5'-AMP was the best substrate; for the remaining T cell types pNPP was preferred); 3) specific inhibition of 5'-nucleotidase by alpha-beta methylene ADP at optimal pH (B type cells exhibited 50% inhibition between 10 and 300 uM, whereas T type membranes required greater than 1 milliM); and 4) inhibition by EDTA at pH optimum (for B derived and Lut 13 membranes, inhibition of 5'-AMP hydrolysis occurred between 0.1 and 5 milliM EDTA, but in T type cells no inhibition was seen). 5'-Nucleotidase was found to be present on Abelson virus transformed lymphomas, plasmacytomas, and LPS stimulated blasts from nu/nu spleen, but on no thymomas except Lut 13. 5'-Nucleotidase could be a key enzyme in the purine metabolism of B cells, but not in T cells. (50 Refs)

74. TUMOR PROMOTING AGENTS.

Tsilimigras CW
Natl. Inst. for Virology, Private Bag X4, Sandringham, Johannesburg 2131, South Africa
S Afr J Sci; 77(3):100-103 1981

The effects of tumor promoting agents, particularly the phorbol ester 12-O-tetradecanoyl-phorbol-13-acetate (TPA) on cells in vitro are considered. The major diterpene ester of croton oil, TPA has been shown to be the most potent promoter of multiple skin tumors in vivo. It has also been found to induce many different responses in vitro, including enhancement of transformation, stimulation of a number of specific enzymes and cyclic nucleotides, modifications in macronucleotides, modifications in macromolecular synthesis, an inhibition of terminal differentiation, changes in cellular membranes and cellular morphology, and disturbances of the transport of cations and small molecules through membranes. TPA has been reported to enhance the degree of the in vitro transformation of fibroblast cell cultures and rat embryo cells previously exposed to polycyclic aromatic hydrocarbons, UV light, or adenoviruses. TPA has also been found to enhance the expression of transformation by Rous sarcoma virus in chick embryo fibroblasts. TPA had been shown to induce ornithine decarboxylase, protease, and plasminogen activator. TPA seems to stimulate DNA and RNA synthesis. Other classes of possible tumor promoters, such as melittin, phenol, oleic acid, some non-aromatic hydrocarbons, Tween 60, saccharin, and cyclamate, are discussed. (16 Refs)

75. LYMPHOCYTE HYBRIDOMAS IN CANCER RESEARCH: EARLY HISTORY.

Sinkovics JG
2336 North Braeswood, Houston, TX, 77030
J Med; 12(2):109-126 1981

Research conducted since the early 1960's on the fusion of murine leukemia virus-producing cells and antibody-producing plasma cells is reviewed. The tissue culture of a diploid, Rauscher virus-producing lymphoma (620) yielded tetraploid lymphoma cells, because the tumor attracted immune plasma cells in vivo and fusion between a lymphoma cell and an immune plasma cell took place in culture. A cell line (818) established from the fused cells continued to produced leukemia virus and a specific antibody directed to the virus. This phenomenon was reproduced in in vitro and in vivo by cocultivation, or by inoculation into mouse peritoneal cavities, of 620 lymphoma cells and normal spleen cells from leukemia virus immune mice. The preparation of monoclonal antibody-producing lymphocyte hybridomas by the fusion of murine plasmacytoma cells (P3X63-Ag8) with immune spleen cells also is described. Technical requirements for the growth of the hybridomas are summarized. The possibility that hybridoma formation occurs in lymphoproliferative disorders (eg, Burkitt's tumors and Hodgkin's disease) is discussed. The Reed-Sternberg clls of Hodgkin's disease could result from the fusion of a neoplastic mononuclear cell with a specific antibody-producing plasma cells; Sezary cells are probably T-lymphocyte hybridomas formed between neoplastic and helper T cells. (46 Refs)

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VIRUS ISOLATION AND CHARACTERIZATION

1. ISOLATION AND CHARACTERIZATION OF A NEW MOUSE MAMMARY TUMOR VIRUS FROM BALB/C MICE.

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Virology; 114(1):175-186 1981

A novel mouse mammary tumor virus (MMTV) has been isolated from mice of a subline of the BALB/cCrl Med mouse strain designated BALB/cV. Whereas breeding females of the parent BALB/cCrl Med colony have a mammary tumor incidence of 1%, 47% of the breeding females of the BALB/cV subline develop mammary tumors before 10 mo of age. Foster nursing experiments demonstrated this virus, termed MMTV (BALB/c), was transmitted only by milk. The novel MMTV isolate was shown to be immunologically related to, but distinct, from the MMTV variants of C3H, GR, and RIII mice by a series of competition radioimmunoassays for the MMTV 28,000-dalton major core protein (p28), and the 52,000 (gp52)-

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and 36,000-dalton (gp36) major envelope glycoproteins. Monoclonal antibodies directed against MMTV gp36 were also used to clearly distinguish MMTV(BALB/c) from MMTV(C3H), MMTV(RIII), MMTV(GR) MMTV(C3HfC57BL), and MMTV(A). MMTV-specific proviral DNA content of mammary adenocarcinomas arising in the BALB/cV subline was examined with restriction endonucleases and the Southern blot technique, and compared to the MMTV proviral DNA content of BALB/cAnDe mammary tumors. The virus arising from these latter tumors has been termed MMTV(O). Analysis of EcoRI digests of high-mol-wt DNA from both types of mammary tumors demonstrated additional MMTV-related proviral sequences when compared to the DNA of normal BALB/c tissues. The patterns generated with the restriction endonuclease SacI distinguished the additional MMTV-specific proviral information in the mammary tumors of the BALB/cV mice from the proviral information in tissues containing the GR, C3H, or RIII MMTVs, as well as from the proviral information in the BALB/cAnDe mammary tumors. These immunological and molecular studies thus define MMTV(BALB/c) as a novel MMTV variant. (Author abstract) (38 Refs)

2. TUMOR VIRUSES OF NONHUMAN PRIMATES.

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Arch Geschwulstforsch; 51(3):242-261 1981

Tumor viruses have been isolated in increasing numbers from nonhuman primates in recent yr. Currently-known viruses are reviewed. Among the DNA viruses, the papovaviruses have been isolated only from Old World monkeys. Adenoviruses have been found in Old and New World monkeys and apes. Alpha-herpesviruses have not been shown to be related to neoplasms. Beta-herpesviruses have been shown to be related to such human viruses as the Epstein-Barr virus. Also discussed are pox viruses and hepatitis B. Among the RNA viruses are several families not considered relevant to tumor research. Among those considered relevant are the Type C and Type D retroviruses. Experimental evidence of the relationships among nonhuman primate viruses and with human viruses is useful in determining the etiology of human viruses. (134 Refs) (In GER)

VIRUS ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

3. INCREASED PHOSPHOTYROSINE CONTENT AND INHIBITION OF PROLIFERATION IN EGF-TREATED A431 CELLS.

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Nature; 293(5830):305-307 1981

The effect of epidermal growth factor (EGF) on phosphotyrosine content of exponentially growing A431 human epidermoid carcinoma cells was determined by labelling cells to equilibrium with 32P-orthophosphate, treating replicate plates 3 hr with EGF, and measuring phosphotyrosine. EGF increased phosphotyrosine content 7x from 0.02 to 0.14% of cellular phosphoamino acids, indicating that EGF activates tyrosine-specific protein kinase activity in vivo as it does in vitro and the kinase activity is an important component of the mechanism of EGF action. In contrast to Rous sarcoma virus (RSV) transformation, EGF inhibits replication of A431 cells. No growth was apparent when A431 cells were maintained with saturating concentrations of EGF over a 14-day period. Affinity of EGF receptors for EGF was inversely related to cell density. The measured equilibrium dissociation constant, Kd, for EGF binding at low and high cell densities was higher than the half-maximally effective concentration, EC50, of EGF required to inhibit cell proliferation at that cell density (7x at 500 cells/square cm and 4x at 15,000 cells/square cm). Occupancy of only a fraction of EGF receptors seems to be required for growth inhibition. Dose-response of growth inhibition was strongly affected by tissue culture substratum. (36 Refs)

4. CYTOGENESIS OF MURINE MAMMARY TUMORS IN BALB/CFC3H AND BALB/CFRIII STRAINS.

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Histochemistry; 72(1):49-53 1981

The C3H and RIII variants of the murine mammary tumor virus show different biological behavior and morphology in BALB/cf mice that carry these strains, but the mechanism of these differences is not known. The involvement of two different mammary cell types must be considered: epithelial and myoepithelial cells. Four tumors from each of the two strains (BALB/cfC3H and BALB/cfRIII) were processed to test the ATPase activity of their plasma membranes: tumor fragments were fixed, washed, embedded, sectioned, and incubated in one of two media, the first capable of demonstrating a Mg++-dependent ATPase (which is present on the plasma membranes of both epithelial and myoepithelial cells) and the second capable of demonstrating a Na+/K+-dependent ATPase (which is present only on the plasma membrane of myoepithelial cells). Electron microscopic examination, of the specimens showed viral particles of both A and B types present but distributed differently in tumors of the two strains. The histochemical results were (1) both types of tumor fragment showed Mg++-dependent but not Na+/K+-dependent ATPase activity on the cells' plasma membranes, (2) no positive reaction was seen in tissue incubated without ATP, and (3) no differences were seen in positive cases between tissue stained with uranyl acetate alone and those stained with uranyl acetate and lead citrate. These results suggest that myoepithelial cells do not participate in the growth of the tumors studied here. (11 Refs)

5. NEW CELL SURFACE GP70 RELATED TO FRIEND MINK CELL FOCUS-INDUCING VIRUS IS EXPRESSED ON FRIEND VIRUS-INDUCED ERYTHROLEUKEMIC SPLEEN CELLS AFTER ELIMINATION OF ECOTROPIC FRIEND VIRUS GP70 IN RFV-3R/S MICE.

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J Exp Med; 154(3):868-882 1981

The expression of individual Friend virus (FV)-encoded proteins in FV leukemic spleen cells was studied at various times in the course of FV leukemia in order to determine the role of anti-FV antibody in altering the expression of viral antigens and infectious virus release in these cells. The results indicated that the presence of anti-FV antibody late in the disease is associated with a decreased expression of Friend helper virus (FMuLV)-encoded intracellular and cell surface proteins, whereas the expression of the replication-defective spleen focus-forming virus (SFFV)-encoded proteins appears to be minimally altered. This selective loss of F-MuLV proteins appeared to correlate with the specificity of the mouse anti-FV antibody that was found to recognize F-MuLV but not SFFV-specific proteins. In addition, a new gp70 molecule was identified on the surface of FV leukemic spleen cells late in the disease. This molecule differed from gp70 in the ecotropic Friend virus, which was inoculated into these mice, in that it shares cross-reactivity with Friend mink cell focus-inducing virus. The potential importance of this recombinant is discussed. (32 Refs)

6. FRIEND DISEASE IN VITRO.

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J Exp Med; 154(3):594-608 1981

Data on the results of polycythemia-inducing spleen focus-forming (SFFVp) helper-independent Friend murine leukemia virus (F-MuLV) infection are presented. The ability to produce SFFVp (F-MuLV) disease in vitro was studied. The polycythemia-inducing strain of Friend leukemia virus (FLV-P) regularly induced the production of low but significant levels of morphologically recognizable erythroid cells as well as the production (1 wk after infection) of a large number of erythroid colony-forming units (CFU-E). However, hemoglobinized cells were present only for 8-9 wk after infection, and erythroid progenitor cells could not be detected by 12 wk after infection. Although FLV-P infection generated CFU-E formation and erythropoietin-independent erythropoiesis, this was not sufficient by itself to give a sustained erythropoiesis or to lead to production of tumor cell lines. Infection of noninduced or anemic mouse serum (AMS)-induced cultures with FLV-P did not lead to a marked increase in the hemopoietic stem cells (CFU-S). Infection of AM S-induced (erythroid) cultures with FLV-P gave a biological response consistent with the effects observed in vivo: erythropoiesis occurring concomitantly with a massive production of primitive erythroid cells. This erythroid hyperplasia was maintained for a prolonged period without the necessity of further addition of an erythropoietic stimulus (AMS). (42 Refs)

7. IMMUNOPATHOLOGY OF NATURAL AND EXPERIMENTAL LYMPHOMAS INDUCED BY WILD MOUSE LEUKEMIA VIRUS.

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Am J Pathol; 104(3):272-282 1981

Naturally occurring lymphomas of Lake Casitas (LC) wild mice, and the lymphomas induced by LC murine leukemia virus (MuLV) in Swiss mice from the National Institutes of Health, displayed remarkably similar gross, microscopic, and functional characteristics. They spared the thymus, arose primarily in the splenic red pulp, became leukemic, and were comprised of stem cells lacking classic T- and B-cell markers. Cytoplasmic and surface Ig were undetectable in 34 of 35 spontaneous LC lymphomas and in any of 10 LC MuLV-induced lymphomas in NIH Swiss mice. Assays for Ig secretion, complement (C'3) and Fc receptors, Thy 1.1,2 antigens, Ly 1,2 antigens, and erythroid and myeloid markers were negative on all of the spontaneous and experimental lymphomas. Cell lines were derived from five spontaneous lymphomas of LC mice. Three lines were characterized as null cells, one line as B cells, and one line as macrophages. All cell lines were diploid. The wild mouse spontaneous lymphomas, and lymphomas experimentally induced by LC MuLV in laboratory mice, provide a useful model for childhood acute lymphoblastic leukemia and for study of the early steps of B-lymphocyte differentiation. (Author abstract) (64 Refs)

8. RELATIVE EFFICIENCY OF TEST PROCEDURES TO DETECT LYMPHOID LEUKOSIS VIRUS INFECTION.

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Poult Sci; 60(9):2037-2044 1981

The efficacy of test procedures in the detection of avian lymphoid leukosis virus (LLV) or antigen in various test materials collected from day-old chicks and adult hens was compared. When blood and meconium collected from 297 chicks were assayed for LLV by the phenotypic mixing (PM) test, blood was found to be superior to meconium in identifying newly hatched LLV-infected chicks. When albumin samples from freshly laid eggs were assayed for virus and LLV-group-specific (gs) antigen, 100% concordance was observed for both the PM and direct complement fixation (D-CF) tests. The enzyme-linked immunosorbent assay was found to be more sensitive than the D-CF test in the detection of LLV and GS antigen in the albumin of eggs . A high percentage of agreement was observed when PM and D-CF were used on blood, cloacal swab, and albumin samples collected from adult hens. All hens that were identified as LLV-positive at 28 and 48 wk were also so identified at 19 wk of age. Discrepancies between results obtained with different test procedures were clear. When cloacal swabs and albumin were taken from hens that are producing endogenous virus or those that are producing gs antigen and chick helper factor, but lack complete virus, were tested for gs antigen by the D-CF test, 7/12 of the swabs collected from chickens with endogenous virus were positive for gs antigen. Large amounts of endogenous virus or gs antigen were present in the swabs, but only 1/48 albumin samples were positive. (21 Refs)

9. PHYSICOCHEMICAL AND IMMUNOLOGICAL PROPERTIES OF TISSUE DNA FROM MICE WITH ONCORNAVIRUS-INDUCED LEUKEMIA.

Chamova KG, Perelaznyi AA, Guseva NI
Res. Lab. Experimental Immunobiology, Moscow, USSR
Biull Eksp Biol Med; 91(7):60-62 1981

DNA specimens isolated from the spleen of mice with leukemia induced by Freund leukemia virus or by Rauscher virus were found to contain the antigenic determinants that were absent in the normal homologous DNA. Denaturation of leukemic DNA did not affect its immunologic specificity. (10 Refs) (In RUS)

10. SYNTHESIS OF MRNA GLOBIN IN DISTURBANCES OF ERYTHROID CELL DIFFERENTIATION.

Peresleni TIu, Dvorkin GA
Inst. General Genetics, Moscow, USSR
Dokl Akad Nauk SSSR; 258(6):1492-1495 1981

Synthesis of globin messenger RNA (mRNA) was studied in a culture of erythroblasts transformed by Rauscher virus and in the spleen of mice with Rauscher erythroleukemia. Molecular hybridization of globin complementary DNA with RNA isolated from Rauscher erythroleukemia cells showed virtual absence of globin mRNA. (14 Refs) (In RUS)

11. MYELOID AND ERYTHROID NEOPLASTIC RESPONSES TO AVIAN DEFECTIVE LEUKEMIA VIRUSES IN CHICKENS AND IN QUAIL.

Moscovici C, Samarut J, Gazzolo L, Moscovici MG
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Virology; 113(2):765-768 1981

A comparative study of the oncogenic potential of two avian defective leukemia viruses (DLVs) shows that avian erythroblastosis virus induces myeloid leukemia in quail and confirms that E26 causes erythroid leukemia in chickens. These results indicate that the response of birds to these two DLVs depends on the host species and suggest that classification of DLVs based only on in vitro studies may not be definitive. (Author abstract) (9 Refs)

12. CELL MEMBRANE CHARACTERISTICS AND BIOLOGICAL BEHAVIOR OF VIRUS TRANSFORMED CELLS.

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Klin Wochenschr; 59(17):957-964 1981

The transformation of a normal into a tumor cell is not caused by a single molecular event, but is the consequence of several simultaneous or consecutive molecular processes, which lead to a variety of changes in the structure and the metabolism of the cell. Investigations with the Rous sarcoma virus show that a single gene is primarily responsible for these changes that is coding for a phosphoprotein which, however, is multifunctional. The biochemical and biologic events which initiate and maintain the transformed status of the cell involve mainly the cytoplasmic membrane. At both the outer and the inner surface of the cell membrane dramatic changes occur which influence the cell structure, permeability of the cytoplasmic membrane, and the intracellular metabolic pathways. Most probably, these transformation-associated events are also involved in cell proliferation under physiologic conditions. In the tumor cell, however, they are not further regulated physiologically, with the consequence of an uncontrolled and incessant cell division. (Author abstract) (30 Refs) (In GER)

13. F-ACTIN AGGREGATES IN TRANSFORMED CELLS.

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J Cell Biol; 90(3):797-802 1981

Polymerized actin has been found aggregated into distinctive patches inside transformed cells in culture. The F-actin-specific fluorescent probe, nitrobenzoxadiazole-phallacidin, labels these F-actin aggregates near the ventral cell surface of cells transformed by RNA or DNA tumor viruses, or by chemical mutagens, or spontaneously. Their appearance in all eight transformed cell types studied suggests their ubiquity and involvement in transformation morphology. Actin patches developed in normal rat kidney (NRK) cells transformed by a temperature-sensitive mutant of Rous sarcoma virus (LA23-NRK) within 30 min after a shift from the nonpermissive (39 C) to the permissive temperature (32 C). Patch appearance paralleling viral src gene expression tends to implicate pp60src kinase activity in destabilizing the cytoskeleton. However, appearance of the actin aggregates in cells not transformed by retrovirus calls for alternative mechanisms, perhaps involving an endogenous kinase, for this apparently common trait. (Author abstract) (26 Refs)

14. TRANSFORMATION-ENHANCING ACTIVITY OF GELATIN-BINDING FRAGMENTS OF FIBRONECTIN.

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Dept. Virology, Univ. Helsinki, 00290 Helsinki 29, Finland
Proc Natl Acad Sci USA; 78(8):4965-4969 1981

Studies have established that cryoprecipitates of the plasma of tumor patients contain a biological activity enhancing morphological cell transformation (transformation-enhancing factor; TEF) in cultures of chicken embryo fibroblasts infected with temperature-sensitive mutants of Rous sarcoma virus. We report here that similar TEF activity is effected by defined fragments of human plasma fibronectin obtained by limited digestion with major humoral or tissue proteinases. TEF activity was obtained from plasminolytic fragments of fibronectin and from cathepsin G-treated fibronectin. No activity was recorded from intact dimeric fibronectin or its reduced and alkylated subunits, from fibrinogen or its plasminolytic fragments, or from plasmin (EC 3.4.21.7) or cathepsin G (EC 3.4.21.20) treated or untreated with proteinase inhibitors. All of the TEF activity of the proteolytic fragments of fibronectin was located on the gelatin-binding peptides. The minimum effective doses in the TEF assay were 750 ng/ml of plasmin-treated fibronectin, 100 ng/ml of gelatin-binding plasminolytic fibronectin (enriched in Mr 180,000-190,000 polypeptides), and 100 ng/ml of gelatin-binding fragments of cathepsin G-treated fibronectin (enriched in a Mr 30,000 fragment). TEF activity of proteinase-treated fibronectin was inhibited by gelatin and by intact dimeric fibronectin. The potent TEF activity of proteolytic fragments of fibronectin raises the possibility that they may have a role in malignant transformation. (Author abstract) (32 Refs)

15. EFFECTS OF VIRAL TRANSFORMATION ON SYNTHESIS AND SECRETION OF COLLAGEN AND FIBRONECTIN-LIKE MOLECULES BY EMBRYONIC CHICK CHONDROCYTES IN CULTURE.

Yoshimura M, Jimenez SA, Kaji A
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J Biol Chem; 256(17):9111-9117 1981

Monolayer cultures of chondrocytes isolated from 11-day-old chick embryo vertebral cartilage were transformed by Rous sarcoma virus, and the effects of transformation on synthesis and secretion of extracellular proteins by these cells were studied. Transformation resulted in decreased synthesis of Type II collagen which did not appear to be due to underhydroxylation of collagenous protein but to a decrease in the total amount synthesized. Carboxymethyl-cellulose chromatography and polyacrylamide disc gel electrophoresis failed to demonstrate any alpha2 chains as a result of the transformation, suggesting that conversion of Type II to Type I collagen did not occur. In contrast to the decrease in collagen synthesis, synthesis of a molecule with biochemical characteristics similar to fibronectin increased markedly in virally transformed cultures. Although there were no significant differences in the amount of fibronectin-like molecules in the cell layers of normal and transformed chondrocytes, a marked increase of these molecules in the culture media of the transformed cells was demonstrated. These findings were confirmed by experiments with temperature-sensitive mutants of the virus. (Author abstract) (37 Refs)

16. TEMPERATURE-DEPENDENT AND TRANSFORMATION-ASSOCIATED CHANGES IN POLYAMINE METABOLISM IN NORMAL AND ROUS SARCOMA VIRUS-INFECTED CHICK EMBRYO FIBROBLASTS.

Holtta E, Vartio T, Janne J, Vaheri A, Hovi T
Dept. Virology, Univ. Helsinki, SF-00170 Helsinki 17, Finland
Biochim Biophys Acta; 677(1):1-6 1981

Tertiary cultures of chick embryo fibroblasts infected and transformed by the wild-type Rous sarcoma virus, when actively growing at 35 C, had higher putrescine levels than the respective uninfected cells. Transformed cells also had much higher specific activity of ornithine decarboxylase (EC 4.1.1.17) than the normal fibroblasts. At 41 C the difference in putrescine levels between the normal and the transformed cells was less marked, and both cell types showed a relative accumulation of spermine. Cultures infected with the NY68 mutant virus, which is temperature-sensitive for transformation, showed a 41 C normal cell morphology and intermediate polyamine pattern, while at 35 C a transformed phenotype was found in both aspects. In shift-down experiments a change towards the permissive temperature pattern of polyamine metabolism was evident within 2-3 hr. Difluoromethylornithine, a specific and irreversible inhibitor of ornithine decarboxylase efficiently reduced the enzyme activity as well as the levels of both putrescine and spermidine in all culture types and temperatures. Incubation of Rous sarcoma virus-transformed cells with 3 mM difluoromethylornithine for 36 hr did not affect the maintenance of the transformed state. Likewise, when NY68-infected cultures were exposed to difluoromethylornithine at 41 C for 12 hr and then shifted down to 35 C, the appearance of the transformed morphology took place concomitantly with that of the control cultures without respective changes in the polyamine levels. This suggests that the transformation-associated pattern of polyamines in chick embryo fibroblasts is not a prerequisite for morphological transformation of these cells. (Author abstract) (27 Refs)

VIRUS REPLICATION AND EXPRESSION

17. PHORBOL ESTER-INDUCED EXPRESSION OF PRIMATE RETROVIRUSES.

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Arch Geschwulstforsch; 51(7):615-622 1981

The 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced expression of simian retroviruses of type C (BaEV, SSV) or type D (MPMV) and of a type D isolate derived from a human cell line (PMFV) was studied in four human cell lines (Tu 197, HEK, E1, and A 204). TPA caused a significant but transient increase in the virus production and cytomorphological changes in the cell lines Tu 197, HEK, and E1, but not in A 204. The stimulation of the virus production reaches its max on days 2-3, at which time the virus production was 15-30x higher than in controls. The optimal TPA concentration was 5-10 nanog/ml. Higher and lower concentrations had a much weaker stimulating effect. (25 Refs) (In GER)

18. CHARACTERIZATION OF THE BONE MARROW CELL POPULATION EXPRESSING AN AKR MURINE LEUKAEMIA-VIRUS GP71-LIKE ANTIGEN.

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Immunology; 44(2):339-345 1981

The murine bone marrow population mainly responsible for the unique competing activity of this lymphoid organ in the competition radioimmunoassay (cRIA) for AKR murine leukemia viruses gp71 has been partially purified and characterized. That population could be distinguished by the following properties: (i) gp71+ cells (cell population expressing the AKR MuLV gp71 antigen) are mainly medium density cells, according to their distribution in the layers of a discontinuous bovine serum albumin (BSA) gradient; (ii) The gp71 positive cells are not mature lymphocytes; (iii) This cell population is found both in the FcR+ and FcR- compartments and is not included in the complement (C') receptor-positive population; and finally, (iv) the gp71+ cells are phagocytic cells and an adherent cell population according to its capacity to adhere to plastic surfaces, nylon wool and Sephadex G-10. (Author abstract) (25 Refs)

19. CORRELATION BETWEEN THE PRESENCE OF NATURAL ANTITUMOR ANTIBODIES AND ACTIVATION OF MULV ENDOGENOUS VIRUS IN BALB/C MICE.

Menard S, Colnaghi MI, Tagliabue E
Istituto Nazionale Tumori, Via G. Venezian 1, 20133 Milano, Italia
Tumori; 67(4):283-292 1981

Individual 3-mo-old or 12-mo-old BALB/c mice, as well as 5-mo-old nu/nu or nu/+ BALB/c mice, showed a direct correlation between the serum level of natural antitumor cytotoxic antibodies and the capacity of spleen cells to infect SC-1 cells permissive for murine ecotropic viruses. Pooled or individual sera from 3-mo-old BALB/c mice, negative for the presence of natural antitumor cytotoxic antibodies and whose spleen cells were unable to infect the SC-1 cells, were negative both for SC-1 cells and SC-1 cells infected by MuLV. On the contrary, pooled or individual sera from 15-mo-old BALB/c mice, positive for the presence of natural antitumor antibodies and with infecting spleen cells, were cytotoxic for infected SC-1 cells but not for the uninfected ones. The infection of SC-1 cells by MuLV could be inhibited by 3-mo-old spleen cells, and this effect was suppressed by depriving the inhibiting spleen cells of T cells by means of an anti-Thy-1 antibody plus complement. The cells with infectious capacity did not belong to the T-cell compartment, as demonstrated by the lack of infection after passing the infecting spleen cells through an anti-Ig column, whereas T-deprivation did not modify the infectious capacity. A natural anti-gp 70 monoc lonal antibody, which exerted a complement-dependent cytotoxic effect on tumor cells, strongly inhibited the infection of the permissive SC-1 cells by MuLV. (Author abstract) (24 Refs)

20. RETROVIRUS GENE EXPRESSION DURING THE CELL CYCLE. I. VIRUS PRODUCTION, SYNTHESIS, AND EXPRESSION OF VIRAL PROTEINS IN RAUSCHER MURINE LEUKEMIA VIRUS-INFECTED MOUSE CELLS.

Balazs I, Caldarella J
Genetics and Molecular Biology Unit, Graduate Sch., Sloan-Kettering Inst. for Cancer Res., New York, NY, 10021
J Virol; 39(3):792-799 1981

Synchronized mouse cells (JLS-V9) chronically infected with Rauscher murine leukemia virus were used to study virus production, the synthesis of gag and env precursor proteins, and the expression of env protein on the cell surface during the cell cycle. The amount of virus released into the medium by synchronized cells during a 30-min interval was determined by using the XC plaque assay and by measuring reverse transcriptase activity. The results show that virus production occurs during mitosis. Labeling of the cell surface of synchronized cells with 125I or with fluorescein-conjugated antiserum shows that the amount of gp70env on the cell surface parallels cellular growth. Therefore, the cell cycle-dependent release of virus is not accompanied by similar variations in the amount of viral envelope protein on the cell surface. Immunoprecipitation of cells labeled with [35S]methionine, followed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, was used to measure viral protein synthesis during the cell cycle. The rate of synthesis of gag precursor proteins show three max corresponding to the G1, middle S, and late S to G2 phases of the cell cycle. The rate of synthesis of env precursor proteins does not change, suggesting that in these cells the synthesis of these two gene products is controlled separately. (Author abstract) (28 Refs)

21. HATCHERY-RELATED CONTACT TRANSMISSION AND SHORT-TERM SMALL-GROUP-REARING AS RELATED TO LYMPHOID-LEUKOSIS-VIRUS-ERADICATION PROGRAMS.

Fadly AM, Okazaki W, Witter RL
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Avian Dis; 25(3):667-677 1981

Pathogen-free chickens of a cross highly susceptible to lymphoid leukosis virus (LLV) were examined to determine (1) the rate of transmission of LLV from congenitally infected chicks to uninfected chicks in the hatcher and the concomitant effect of manual vent sexing on this transmission, (2) the rate of contact transmission of LLV in chickens reared on a wire-mesh floor compared with that in chickens reared on a solid floor, and (3) the efficiency of short-term small-group-rearing in brooding battery and colony cages in preventing LLV transmission from infected to uninfected groups of chicks. In the first experiment, susceptible chicks exposed only in the hatcher were not LLV infected when tested for virus and antibody at 16 wk; however, 37/39 susceptible chicks exposed at hatching and then manually vent-sexed on the day of hatch and then reared in isolation had LLV-neutralizing antibody in their sera, and the rate of transmission varied directly with the length of time that contact exposure continued after hatching. In the second experiment, rearing chickens on a solid floor enhanced the rate of contact transmission of LLV; when examined at 16 wk, chickens raised on the wire-mesh floor had a lower incidence of infection (p less than 0.01) than those reared on the solid floor. In the third experiment, the indirect contact between infected and uninfected susceptible chicks did not result in transmission of LLV. These results indicate that intimate direct contact is necessary for the rapid transmission of LLV from infected to uninfected chicks. (25 Refs)

22. ESTIMATION OF MOUSE MAMMARY TUMOR VIRUS GP52 ABUNDANCE BY PROTEIN A ASSAY: A COMPARISON OF VIRAL ANTIGEN EXPRESSION ON C3H AND GR MAMMARY TUMOR CELLS.

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Intervirology; 15(2):111-120 1981

An adherent cell isotopic staphylococcal protein A test (ISPAT) was used to estimate the abundance of mouse mammary tumor virus (MMTV) gp52 cell surface antigen (CSA) on mammary tumor cells. Protein A assays were first utilized, not strictly as a means of antigen detection, but as a means to determine the kinetics of dexamethasone-mediated changes in gp52 cell surface expression. Results indicated increases in gp52 CSA within 4 hr of dexamethasone treatment and max levels of antigen expression within 12-24 hr after treatment. Comparison of gp52 determinants on dexamethasone-stimulated mammary tumor cells demonstrated a greater abundance on C3H Mm5mt/cl than on GR-MMTV cultures. Parallel antigen assays with gp52 and Rauscher murine leukemia virus (R-MuLV) antisera demonstrated that GR-MMTV cells expressed fewer C-type determinants and thus a more preferential expression of gp52 determinants than other cell lines tested. The gp52/R-MuLV binding ratio was only 2.4:1 for C3H cultures in contrast to 5.7:1 for GR cultures. In addition, a comparison of gp52 expression on viral producer and nonproducer cells provided a quantitative estimate of the extent of expression which occurred in a retrovirus nonproducer culture. Results of ISPAT demonstrated that 75% of the gp52 detected on producer cells was present on nonproducer cultures. Comparison of the expression of gp52 CSA and the release of gp52 into culture fluids during hormone treatments demonstrated that both assays (ISPAT and gp52 radioimmunoassay) detect and quantitate coordinate changes in the expre ssion and release of MMTV gp52. In antibody excess, protein A assays provided quantitative estimates of CSA abundance not offered by alternative methods of CSA detection. (Author abstract) (17 Refs)

23. RAPID EMERGENCE OF MINK CELL FOCUS-FORMING (MCF) VIRUS IN VARIOUS MICE INFECTED WITH NB-TROPIC FRIEND VIRUS.

Ishimoto A, Adachi A, Sakai K, Yorifuji T, Tsuruta S

Dept. Biophysics, Inst. Virus Res., Kyoto Univ., Sakyo, Kyoto 606, Japan

Virology; 113(2):644-655 1981

Mink cell focus forming (MCF) virus was always detected in the enlarged spleens of NFS, BALB/c, SL, and C3H mice infected with NB-tropic ecotropic Friend virus. The MCF virus emerged from the spleens as early as 7 days postinfection. The MCF viruses isolated from various mouse strains were NB-tropic dualtropic and highly oncogenic to newborn NFS and BALB/c mice. When cells infected with MCF virus were overlaid with XC cells without UV irradiation, the viruses were XC positive. Interference and host-range properties suggested that the MCF viruses were recombinants between exogenous NB-tropic ecotropic Friend virus and endogenous xenotropic virus. (Author abstract) (29 Refs)

24. CHARACTERIZATION OF SARCOMA-POSITIVE, LEUKEMIA-NEGATIVE (S+L-) HUMAN CELLS INDUCED BY THE FELINE LEUKEMIA VIRUS PSEUDOTYPE OF MOLONEY SARCOMA VIRUS.

Rhim JS
Lab. Cellular and Molecular Biology, NCI, NIH, Bethesda, MD, 20205
Proc Soc Exp Biol Med; 167(4):597-606 1981

The isolation and characterization of sarcoma-positive, leukemia-negative (S+L-) human cells induced by the feline leukemia virus pseudotype of Moloney sarcoma virus (Mo-MSV(FeLV)) is reported. The four clones selected for study were negative for infectious virus and type C virus particles, but, contained a rescuable MSV genome and murine leukemia virus (MuLV)-specific antigen, such as the gag gene products, p15, p12, and p30, and lacked the env gene protein (gp 70). The cells were all tumorigenic in nude mice. In human, NRK, and NIH 3T3 mouse embryo cells, the Mo-MSV rescued by baboon type C virus (M-7), Mo-MSV(M-7), readily produced foci. Human cells transformed by MoMSV(M-7) were virus producers, while Mo-MSV(M-7)-transformed NRK and NIH 3T3 mouse embryo cells were S+L- cells. These latter cells were negative for infectious virus but contained a rescuable MSV genome and MuLV antigen. (21 Refs)

25. ABILITY OF VACCINIA VIRUS TO INDUCE EXPRESSION OF RETRAVIRUS P30 IN CONTINUOUS MICE CELL LINES.

Merekalova ZI, Mazurenko NP, Rapp F, Turner N
Lab. Virus Carcinogenesis, Cancer Res. Center, Moscow, USSR
Biull Eksp Biol Med; 91(6):710-712 1981

Ability of vaccinia virus to induce expression of the major structural protein p30 of Rauscher leukemia virus (RLV) and Moloney sarcoma virus was studied in mice continuous cell lines (NclAc 1 10 and 3T3 BALB). Immunoperoxidase technique showed marked fluorescence in cells infected with RLV and vaccinia virus. (13 Refs) (In RUS)

26. COCARCINOGENIC EFFECT OF VACCINIA VIRUS AND HERPES SIMPLEX VIRUS IN TISSUE CULTURE.

Mazurenko NP, Merekalova ZI, Pavlish OA, Bykovskii AF, Kurtsman MIa, Mazurenko NN
All-Union Cancer Res. Center, Moscow, USSR
Vestn Akad Med Nauk SSSR; (7):3-10 1981

Cocarcinogenic effect of vaccinia virus (VV) and herpes simplex virus (HSV) was studied in transplantable murine cell lines. The cultured cells of embryonal tissue of BALB/c mice were infected with VV, and the expression of structural protein p30 was assayed by indirect immunofluorescence reaction. Specific cytoplasmatic fluorescence was recorded in 15-20% of cells. Max fluorescence was observed 48-72 hr after infection, which corresponded to the onset of Rauscher leukemia virus replication. HSV-2 caused malignant transformation of BALB/3T3 cells. Inoculation of irradiated BALC/c mice with transformed cells (subclones 333-0 and 333-1) produced tumors in 25% and 80% of the animals. Transformed cells expressed the endogenous murine retrovirus Type 3. (29 Refs) (In RUS)

27. RELATION OF BOVINE LEUKOSIS VIRUS PRODUCTION ON CELL GROWTH CYCLE.

Takashima I, Olson C
Faculty Veterinary Medicine, Hokkaido Univ., Sapporo, Japan
Arch Virol; 69(2):141-148 1981

The cell cycle of fetal lamb kidney (FLK) cultures chronically infected with bovine leukosis virus was synchronized by double thymidine block. The synchronized FLK cells were examined for production of BLV antigen and virion release by cytoplasmic immunofluorescence and syncytia forming assay, respectively. The production of BLV antigens was increased during S and G2 phases and was decreased during M and G1 phases. BLV release was associated with the M phase of FLK cells. Short term lymphocyte cultures from BLV infected cattle were treated with hydroxyurea and mitomycin C. The expression of BLV antigen and DNA synthesis of PHA stimulated lymphocytes was inhibited by both drugs. (Author abstract) (21 Refs)

GENETICS

28. FOUR ROUS SARCOMA VIRUS MUTANTS WHICH AFFECT TRANSFORMED CELL MORPHOLOGY EXHIBIT ALTERED SRC GENE PRODUCTS.

Fujita DJ, Bechberger J, Nedic I
Cancer Res. Lab., Dept. Biochemistry, Univ. Western Ontario, London, Ontario N6A 5B7, Canada
Virology; 114(1):256-260 1981

Four Rous sarcoma virus Schmidt Ruppin A (RSV SR-A) morphf mutants (ST529, WO101, WO201, and WO401), independently isolated in the presence of different mutagens, cause an elongated, or fusiform, transformed cell morphology in chicken embryo fibroblasts at 37 C. The src gene products isolated from cells transformed by these mutants exhibited an apparent mol wt (Mr) of approx 54,000 to 55,000 on SDS-polyacrylamide gels, in contrast to the approx 59,000 to 60,000 Mr pp60src species isolated from wt SR-A-transformed cells, using the same extraction conditions. This difference was observed both in extraction buffers containing SDS, sodium deoxycholate, and NP-40, as well as in buffers not containing SDS and sodium deoxycholate. Partial protease digestion experiments indicated that src gene products of all four mutants were lacking peptides present in the N-terminal half of wt pp60src. The mutant src species isolated from cells transformed at 37 C exhibited kinase activity; in the case of the temperature-sensitive mutant ST529, this activity displayed a pronounced in vitro temperature sensitivity. These results strongly suggest that a common, or similar, structural alteration in 'pp60src' species of the mutants is intimately related to, and perhaps the cause of, the morphf phenotype exhibited by the cells they transform. (Author abstract) (25 Refs)

29. FRIEND MURINE LEUKEMIA VIRUS-INDUCED LEUKEMIA IS ASSOCIATED WITH THE FORMATION OF MINK CELL FOCUS-FORMING VIRUSES AND IS BLOCKED IN MICE EXPRESSING ENDOGENOUS MINK CELL FOCUS-INDUCING XENOTROPIC VIRAL ENVELOPE GENES.

Ruscetti S, Davis L, Feild J, Oliff A
Lab. Tumor Virus Genetics, NCI, NIH, Bethesda, MD, 20205
J Exp Med; 154(3):907-920 1981

The susceptibility of various strains of mice to disease induced by Friend murine leukemia virus (F-MuLV) was studied. The viruses and viral proteins expressed in the spleens of infected and uninfected mice were characterized. An attempt was made to determine if the Friend mink cell focus-inducing virus (Fr-MCF) induces the same disease. It was found that the erythroproliferative disease developing in susceptible F-MuLV-infected mice is correlated with the expression of mink focus-inducing virus (MCF)-related envelope glycoproteins and that MCF viruses isolated from these mice are moderately pathogenic when infected as pseudotypes prepared by mixed infection with either ecotropic or amphotropic MuLV. MCF/xenotropic virus-related envelope protein was expressed in cells from uninfected, resistant but not susceptible strains of mice, which may represent the basis for resistance to F-MuLV disease. (45 Refs)

30. SELECTIVE HOST RANGE RESTRICTION OF GOAT CELLS FOR RECOMBINANT MURINE LEUKEMIA VIRUS AND FELINE LEUKEMIA VIRUS TYPE A.

Fischinger PJ, Thiel HJ, Blevins CS, Dunlop NM
Lab. Viral Carcinogenesis, NCI, Frederick, MD, 21701
J Virol; 39(3):981-985 1981

We isolated a strain of normal goat fibroblasts which was uniquely selective in that it allowed the replication of xenotropic murine leukemia virus but not polytropic recombinant murine leukemia virus. In addition, feline leukemia virus Type A replication was severely diminished in these goat cells, whereas feline leukemia virus Type B and feline endogenous RD114-CCC viruses replicated efficiently. No other known cells exhibit this pattern of virus growth restriction. These goat cells allow the study of xenotropic murine leukemia virus in mixtures which also contain recombinant murine leukemia virus and may be helpful in eliminating feline leukemia virus type which often coexists in feline sarcoma or leukemia virus mixtures with other feline leukemia virus types. (Author abstract) (25 Refs)

IMMUNOLOGICAL STUDIES

31. IMMUNOPREVENTION OF FRIEND VIRUS-INDUCED ERYTHROLEUKEMIA BY VACCINATION WITH VIRAL ENVELOPE GLYCOPROTEIN COMPLEXES.

Hunsmann G, Schneider J, Schulz A
Forschergruppe Tumorimmunologie, D-7800 Freiburg, W. Germany
Virology; 113(2):602-612 1981

Adult STU mice were repeatedly immunized with aggregates of Friend virus envelope glycoprotein gp85. The antigen was given emulsified in incomplete Freund's adjuvant. After the last boost, animals were challenged with a dose of FLV inducing fatal erythroleukemia in 90-100% of the controls. Twenty of 20 mice immunized with 100 ug of gp85 were completely protected, while 3 of 7 animals vaccinated with 10 ug of gp85 died of leukemia. Smaller doses were ineffective, as was the adjuvant alone. Only animals that had developed a strong antibody response survived the FLV challenge. Serum antibodies of these animals reacted with type-, species-, and interspecies-specific determinants of pg85. Only a marginal cellular reactivity to gp85 was detected. The development of viremia was monitored by the use of radioimmunoassay for the internal viral core polypeptide p30. Animals completely protected were not viremic later than 7 days post-FLV infection. Those mice of the immunized groups which died in spite of an early antibody response showed a sharp decrease in serum antibodies to gp85 and a simultaneous appearance of virus in blood about 2-4 wk before death from leukemia. Thus, the suppression of virus spread by antibody seems to be important for immuno-prevention of this virus-induced leukemia. (Author abstract) (26 Refs)

32. ADOPTIVE IMMUNOTHERAPY AND COMBINED CHEMO-IMMUNOTHERAPY IN TRANSPLANTABLE LEUKAEMIA OF AKR MICE (TAL); OCCURRENCE OF NATURAL KILLERS.

Schneiberg K, Rytwinski K, Tabenska J
Instytut Onkologii, Oddzial w Gliwicach, ul. Armii Czerwonej 15, 44-010 Gliwice, Poland
Haematologia (Budap); 14(2):137-146 1981

Inbred AKR mice received transplantable AKR leukemia (TAL: 10(4)-10(5) viable lymph node cells from ill syngeneic donors) by ip injection. Effector cells were obtained from C57BL/6, DBA/2J, BALB/c, or syngeneic AKR donors. Some allogeneic donors had been preimmunized with AKR cells. Some recipients received donor cells irradiated before injection. Some received whole-body x-ray irradiation (300 rad) before injection of tumor cells. Intact mice injected with TAL, but not otherwise treated, survived longer than irradiated mice. Injection of allogeneic effector cells from non-immunized mice increased the survival time of intact TAL-bearing mice. Syngeneic effector cells had no effect. Thymocytes from non-immunized donors or lymph node cells from immunized donors increased survival time in irradiated mice. Injection of 50 mg/kg cyclophosphamide (CY) produced a 70% permanent survival rate. Injection of effector cells did not increase the effect of CY. Thymocytes from immunized or non-immunized donors increased survival time of mice not given CY. Mean survival increased as effector cell:target cell ratio increased from 10:1 to 1,000:1. Above 1,000:1 no increase was noted. Results indicate the existence of natural non-immune cytotoxic cells, directed against Gross virus-infected cells, in C57BL/6, DBA/2J, and BALB/c mice, but not in AKR mice. These effector cells were present in many lymphoid organs. (31 Refs)

33. G(ERLD): A CELL SURFACE ANTIGEN OF THE MOUSE RELATED TO XENOTROPIC MULV DEFINED BY NATURALLY OCCURRING ANTIBODY AND MONOCLONAL ANTIBODY. RELATION GIX, G(RADA1), G(AKSL2) SYSTEMS OF MULV-RELATED ANTIGENS.

Obata Y, Stockert E, DeLeo AB, O'Donnell PV, Snyder HW, Old LJ
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
J Exp Med; 154(3):659-675 1981

G(ERLD), one of the gp70-related cell surface antigens of murine leukemia virus (MuLV), is described and its features compared with the characteristics of other gp-70-related cell surface antigens, GIX, G(RADA1), and G(AKSL2). Sera from hybrid mice of crosses between B6 and 129, and their GIX congenic partners, B6-GIX+ and 129-GIX-, were tested for naturally occuring cytotoxic antibodies against a panel of transplanted tumor lines. Some sera were found to have high cytotoxic activity against ERLD, an x-ray-induced leukemia of B6 origin, as well as against other tumors. The G(ERLD) specificity was identified. The strain distribution of G(ERLD) was distinct from any known cell surface antigens. Quantitative differences in G(ERLD) expression characterized G(ERLD)+ strains. Most GIX+ strains were G(ERLD)+, while most GIX- negative strains were G(ERLD)-. Hybrids between G(ERLD)+ and G(ERLD)- strains expressed approx half the quantity of G(ERLD) found in the G(ERLD)+ parent. G(ERLD) was expressed in G(ERLD)+ mouse strains and in some G(ERLD)- strains. G(ERLD) could be expressed on tumor cells in the absence of other MuLV antigens. The occurrence of natural antibody with high ERLD reactivity was restricted to B6, B6-GIX+, C57L, and hybrid mice of crosses between B6, 129, and GIX congenic partner strains. Experimental results suggested that G(ERLD) expression was controlled by a single locus in B6, by two unlinked loci in 129 and by three unlinked loci in B6-GIX+ mice. It was suggested that one of the loci in 129 and B6-GIX+ mice may be identical or closely linked to the locus controlling GIX antigen expression. Evidence suggested that G(ERLD) is a determinant associated with xenotropic and dualtropic MuLV gp70 molecules, but that it is unstable and tends to be lost during standard purification procedures. A monoclonal antibody to G(ERLD) was produced. (37 Refs)

34. QUANTITATION OF VIRAL ANTIGENS RELEASED INTO PLASMA AND CULTURE FLUIDS BY MURINE MAMMARY TUMOR CELLS.

Ritzi EM, Smith BA, Stolfi RL, Martin DS

Univ. Tennessee Center for Health Sciences, Memphis, TN, 38163

Cancer Res; 41(10):3885-3890 1981

Radioimmunoassays capable of measuring mouse mammary tumor virus (MMTV) mol wt 52,000 envelope glycoproteins (gp52) and mol wt 27,000 proteins (p27) have been used to quantitatively compare plasma concentrations of these viral antigens in mice bearing spontaneous mammary tumors. Although gp52 was detected in the plasma of all tumor-bearing mice tested, p27 was detected in only a portion of tumor-bearing animals. In p27-positive animals, gp52 was detected in higher concentrations than p27. These findings demonstrate that gp52 has preferential utility as a plasma marker for the presence of mammary tumors in MMTV-infected hybrid (BALB/c x DBA/8 F1), Paris RIII, and C3H/HeJ mice. In addition, cultures of MMTV-producing cells [GR-MMTV and MMTV(C3H)Fe1] were used as models to study the release of viral antigens in the absence of serum antibody or additional host factors. Comparisons of extracellular soluble and particulate antigen concentrations demonstrated that gp52 and p27 were present in substantially higher concentrations as soluble than virion-associated antigens. The mean ratio of non-virion-associated gp52 to virion-associated gp52 was 12:5:1 for GR-MMTV cells and 37:3:1 for MMTV(C3H)Fe1 cells. The marked stability of MMTV in culture fluids suggested that virion breakdown was not responsible for the accumulation of soluble viral antigens in culture. The information obtained suggests that abundant virus-free antigens may be of greater use than virion-associated antigens as a source of viral antigen to evaluate mammary tumor status. (Author abstract) (20 Refs)

35. IMPAIRMENT OF IN VITRO GENERATION OF CYTOTOXIC OR T SUPPRESSOR LYMPHOCYTES BY FRIEND LEUKEMIA VIRUS INFECTION IN MICE.

Garaci E, Migliorati G, Jezzi T, Bartocci A, Gioia L, Rinaldi C, Bonmassar E

Inst. Microbiology, Univ. Rome, Piazzale Aldo Moro, 00100 Rome, Italy

Int J Cancer; 28(3):367-373 1981

Spleen cells collected from DBA/2 (H-2d) mice inoculated with the polycythemic variant of Friend-Leukemia Virus Complex (FLV-P) were tested for T-dependent immune functions, such as the in vitro generation of cytotoxic T lymphocytes (CTL) and of non-specific T suppressor lymphocytes (STL). CTL were generated against H-2b splenocytes, and STL were obtained following a 5-day lymphocyte culture wit hout stimulator cells. A progressive and severe impairment of the generation of both CLT and STL was found from 2 wk onward after infection, being almost totally abolished 3-4 wk after virus challenge.. Suppressor cells (SC) capable of inhibiting CTL generation were detected in FLV-P bearing mice. Suppressor activity was unaffected by anti-Thy 1.2 serum and complement but was removed following iron-magnet depletion or passage through nylon-wool column. Moreover complete recovery of the competence of CTL generation was attained when FLV-P infected splenocytes were passed through nylon-wool column. It is concluded that FLV-P infection depresses T-dependent cytotoxic and suppressor responses in mice, by the appearance of non-T adherent phagocytic cells, capable of impairing CTL generation in vitro. (Author abstract) (39 Refs)

36. HETEROLOGOUS TUMOUR GROWTH PATTERNS INDUCED IN RELATED MHC-DEFINED CHICKEN LINES BY SEPARATE ISOLATES OF AN AVIAN SARCOMA VIRUS STRAIN.

Cutting JA, Watanabe DH, Strebel FR, Vogt PK, McBride RA

(c/o McBride) Dept. Pathology, Baylor Coll. Medicine, 1200 Moursund Ave., Houston, TX, 77030

J Immunogenet; 8(4):297-305 1981

Genes within or closely linked to the major histocompatibility complex (MHC) are important to the ability of chickens to regress tumors induced by various strains of avian sarcoma virus (ASV). In an effort to characterize this virus strain-restricted resistance to tumor growth, experiments were performed to seek differential resistance patterns among three closely inbred chicken lines (that differed mainly in that each was homozygous for a different MHC haplotype), using, as tumor inducers, ASV stocks (separate isolates of Subgroup C Bratislava 77 strain) that were more closely related antigenically than those employed heretofore. Different patterns of tumor growth resulted from the inoculation of each isolate into each chicken line. Tumor growth was measured by the parameters of tumor progression (ASV Clone 9 induced tumors that regressed in all three lines, whereas the other two clones induced nonregressing tumors); duration of tumors (all isolates induced tumors with markedly different durations to regression in line G-B1 but with no difference in line G-B3; two clones induced tumors that progressed to host death while the third induced tumors that regressed in line G-B2); and max vol of tumors (in general, the geometric mean of the maxima of tumor volumes induced by the three viral clones in each chicken line could be ranked as follows: Clone 35 greater than H greater than Clone 9). These data suggest that MHC-controlled tumor rejection operates on viral or cellular determinants different from those that define classical viral group or subgroup identity. (16 Refs)

37. DEMONSTRATION OF ANTIGENIC CROSS-REACTIVITY BETWEEN SIMIAN SARCOMA VIRUS (SSV) A ND MASON-PFIZER MONKEY VIRUS (MPMV). BRIEF REPORT.

Micheel B
Central Inst. Cancer Res., Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany

Arch Virol; 69(2):149-153 1981

The reaction of FITC-labeled simian sarcoma virus (SSV) with anti-SSV p30 antibodies conjugated to Sepharose beads is specifically blocked by incubation with antisera to different Type-C virus p30s and also by anti-MPMV p27 serum. (Author abstract) (14 Refs)

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VIRUS ISOLATION AND CHARACTERIZATION

1. ADULT T-CELL LEUKEMIA: ANTIGEN IN AN ATL CELL LINE AND DETECTION OF ANTIBODIES TO THE ANTIGEN IN HUMAN SERA.

Hinuma Y, Nagata K, Hanaoka M, Nakai M, Matsumoto T, Kinoshita KI, Shirakawa S, Miyoshi I
Inst. Virus Res., Kyoto Univ., Kyoto 606, Japan
Proc Natl Acad Sci USA; 78(10):6476-6480 1981

Indirect immunofluorescence of certain human sera demonstrated an antigen(s) in the cytoplasm of 1-5% of the cells of a T-cell line, MT-1, from a patient with adult T-cell leukemia (ATL), which is endemic in southwestern Japan. The antigen was not detected in other human lymphoid cell lines, including six T-cell lines, seven B-cell lines, and four non-T non-B cell

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lines. The antigen did not show cross antigenicity with that of herpesviruses, including Epstein-Barr virus, herpes simplex virus, cytomegalovirus, varicella-zoster virus, herpesvirus saimiri, and Marek disease virus. The proportion of antigen-bearing cells was increased by a factor of approx five on culture in the presence of 5-iodo-2'-deoxyuridine. Antibodies against the antigen in MT-1 cells were found in all 44 patients with ATL examined and in 32 of 40 patients with malignant T-cell lymphomas (most of them had diseases similar to ATL except that leukemic cells were not found in the peripheral blood). The antibodies were also detected in 26% of the healthy adults examined from ATL-endemic areas but in only a few of those examined from ATL-non-endemic areas. On electron microscopy, extracellular Type C virus particles were detected in pelleted MT-1 cells cultured in the presence of 5-iodo-2'-deoxyuridine. (Author abstract) (26 Refs)

2. ISOLATION VIA TRANSFECTION OF FELINE LEUKEMIA VIRUSES FROM DNA OF NATURALLY OCCURRING FELINE LYMPHOMAS.

Rosenberg ZF, Crowther RL, Essex M, Jarrett O, Haseltine WA
(c/o Haseltine) Charles A. Danna Cancer Center, Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Virology; 115(1):203-210 1981

Feline leukemia viruses isolated via transfection from the DNAs of naturally occurring feline lymphoma tissue were compared with viruses representing the three subgroups of FeLV by host range, subgroup, and RNA fingerprinting analyses. A novel host range was observed for two subgroup A viruses obtained from independent tumors. Two distinct viruses with different host ranges, subgroup specificities, and fingerprint patterns were isolated from a third tumor. Although the tumor tissues used in this study were from unrelated cats, the RNA fingerprints of the four transfected viruses demonstrated striking similarities to one another. Approx 88% of the RNase T1 resistant oligonucleotides present in any one isolate are also present in the other three viruses. The transfected viruses share approx 67% of the RNase T1 resistant oligonucleotides found in FeLV subgroups B or C. However, approx 80% of the RNase T1 resistant oligonucleotides of the new virus isolates are found in common with FeLV A/Glasgow 1. (Author abstract) (25 Refs)

3. ISOLATION OF FELINE LEUKEMIA VIRUS FROM A LEOPARD CAT CELL LINE AND SEARCH FOR RETROVIRUS IN WILD FELIDAE.

Rasheed S, Gardner MB
Dept. Pathology, Univ. Southern California Sch. Medicine, 1840 North Soto St., Los Angeles, CA, 90032
JNCI; 67(4):929-933 1981

A strain of feline leukemia virus (FeLV), subgroup A, was isolated in early subpassage of a testicular fibroblast culture obtained from a captive Asian leopard cat. Neither FeLV nor RD-114 virus was recovered from cultured tissues of 15 other animals, representing eight species of wild Fe lidae. (Author abstract) (37 Refs)

4. SOME BIOLOGICAL PROPERTIES OF TWO NEW AVIAN SARCOMA VIRUSES.

Balduzzi PC, Notter MF, Morgan HR, Shibuya M
Dept. Microbiology, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY, 14642
J Virol; 40(1):268-275 1981

The new avian retroviruses UR1 and UR2 were isolated from spontaneous tumors of chickens by cocultivation of tumor material with susceptible chicken embryo fibroblasts. In vitro, UR1 induced formation of small foci of round and fusiform cells. On the other hand, cells infected by UR2 assumed an extremely elongated morphology. In vivo, both viruses induced fibrosarcomas and myxosarcomas with short latencies. Infectivity assays with and without Mitomycin C showed that both viruses were defective for replication, but transformed nonproducing cell clones were obtained only with UR1. UR1-infected transformed nonproducing clones did not release particles detectable by reverse transcriptase assays, and fusion of transformed nonproducing cells with quail cells chronically infected with Rous sarcoma virus (a Bryan strain) failed to rescue infectious virus. This suggested that UR1 does not code for functional envelope glycoproteins. In this regard, UR1 appeared to be similar to Fujinami, PRCII, and Y73 viruses. The helper viruses of partially purified stocks of UR1 and UR2 appeared to belong to subgroup A, but these helper viruses were distinguishable from each other, as shown by host range experiments and neutralization tests. Hybridization studies with DNA complementary to the src gene of Rous sarcoma virus and RNAs extracted from both UR1 and UR2 showed no homology between the genomes of the new isolates and the transforming gene of Rous sarcoma virus. (Author abstract) (29 Refs)

5. BIOLOGICAL PROPERTIES OF ROUS SARCOMA VIRUS ISOLATED FROM TRANSFORMED HAMSTER CELLS.

Cherepantseva EA, Shevliagin VIa
N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR
Vopr Virusol; (4):489-493 1981

The results of comparative evaluation of biological properties of Rous sarcoma virus (RSV) isolated from virogenic hamster 23x cells are reported. RSV isolated from the virogenic cells (RSV-23x) was found to retain the antigenic characteristics of RSV isolated from the original Schmidt-Ruppin cell line (RSV-SR). The RSV-23x induced more effective transformation of mammalian cells than that induced by the RSV-SR. In contrast to the RSV-SR, the RSV-23x was able to reproduce in mammalian cells. (11 Refs) (In RUS)

VIRUS ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

6. SEQUENCE OF EVENTS IN THE TRANSFORMATION PROCESS IN CELLS INFECTED WITH A TEMPERATURE-SENSITIVE TRANSFORMATION MUTANT OF MOLONEY MURINE SARCOMA VIRUS.

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Proc Natl Acad Sci USA; 78(9,part2):5593-5597 1981

Normal rat kidney cells infected with the temperature-sensitive transformation mutant of Moloney murine sarcoma virus were used to study the biochemical and morphological changes that occur during transformation. The infected cells exhibited a normal morphology at the nonpermissive temperature (39 C) and a transformed morphology at the permissive temperature (33 C). A new viral protein was detected 2 hr after shift to the permissive temperature as a polyprotein with an estimated Mr of 85,000 (p85). Scanning electron microscopy of the cells within 5 hr after shifting them to the permissive temperature showed that they became smaller and rounded with numerous elongated microvilli. In an earlier study, changes in hexose uptake were found to occur 8-12 hr after the shift. By 48 hr, the cells had the morphology of a fully transformed cell. Concomitant with the changes in the morphology were alterations in the cytoplasmic microtubule complex. At the nonpermissive temperature, the complex consisted of a lacy network of microtubules. Within 5 hr at the permissive temperature, the lacy network was still present but the microtubules were more diffusely stained and less discernible. By 48 hr, the microtubules were so diffuse that the lacy network could not be recognized. Alterations in the F-actin cables did not occur until 24 hr after shifting the cells to the permissive temperature. Enucleation of the cells at the nonpermissive temperature and shifting the cytoplasts to the permissive temperature did not result in the synthesis of detectable p85 or in any alteration of the cytoplast morphology or microtubule complex, suggesting that the temperature-sensitive lesion affects some event occurring in the nucleus. (Author abstract) (28 Refs)

7. HARVEY AND KIRSTEN SARCOMA VIRUSES PROMOTE THE GROWTH AND DIFFERENTIATION OF ERYTHROID PRECURSOR CELLS IN VITRO.

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Cell; 26(1):91-97 1981

Harvey and Kirsten murine sarcoma viruses have previously been shown to transform fibroblastic cells in culture, and Type C virus pseudotypes of these viruses cause erythroleukemia in susceptible mice. We report a cell culture assay for quantitating the growth-promoting effect of Harvey and Kirsten viruses on erythroid cells. Murine hemopoietic cells were infected in vitro with Harvey or Kirsten sarcoma virus, and then cultured in methylcellulose in the presence of relatively low concentrations of erythropoietin. Under these conditions, large colonies of erythroid cells form in the semi-solid culture media 6 to 8 days after infection. The induction of erythroid bursts was not caused by the murine Type C helper viruses used to pseudotype either Ha-MuSV or Ki-MuSV, or by media from cells carrying the Ki-MuS V and Ha-MuSV genomes. Induction of the erythroid colonies is under genetic control at the Fv1 susceptibility locus, but not at the Fv2 susceptibility locus. A striking feature of the erythroid colonies induced by the Harvey and Kirsten viruses was that they not only proliferated to large size but also differentiated along the erythroid lineage and synthesized Hb. The results indicate that Ha-MuSV and Ki-MuSV can induce proliferation of erythroid precursor cells apparently without interfering with the differentiation program of the cells. The relation between the growth-promoting effect of these viruses on erythroid precursor cells and their ability to induce erythroleukemia is discussed. (Author abstract) (28 Refs)

8. ABELSON LEUKEMIA VIRUS INDUCES LYMPHOID AND ERYTHROID COLONIES IN INFECTED FETAL CELL CULTURES.

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Cell; 26(1):79-89 1981

An examination of Abelson murine leukemia virus (A-MuLV)-hematopoietic cell interaction in cultures of fetal tissues reveals that A-MuLV can stimulate the formation of two different types of colonies. One type of colony is white and composed of A-MuLV-transformed lymphoid cells that can develop into established cell lines. These cells are indistinguishable in morphology from typical adult-derived lymphoid transformants. The second type of colony is pink or red and composed of erythroid cells in various stages of differentiation. Although A-MuLV is required to induce the erythroid colonies, and at least some cells in all of these colonies are infected with the virus, no permanently growing cell lines have been established from the cells in these colonies. The frequency of the two types of colonies varies depending upon the tissue and the gestational age of the embryo. Erythroid colonies are found following infection of early and mid gestation tissues while lymphoid colonies are found following infection of mid and late gestation tissues. Mixing experiments indicate that the two types of colonies arise from distinct target cells. Because A-MuLV mutants that are defective for lymphoid cell transformation are also defective for erythroid colony induction, expression of a functional Abelson protein is probably required for colony induction. Thus A-MuLV is capable of stimulating the cells of two distinct hematopoietic lineages. In one case, infection leads to transformation, while in the second, it leads to growth and differentiation. Both types of interaction are mediated, at least in part, by the same A-MuLV gene product, a molecule previously considered to induce transformation in all stably infected cells. (Author abstract) (61 Refs)

9. ONTOGENY OF ABELSON MURINE LEUKEMIA VIRUS TARGET CELLS.

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Haematol Blood Transfus; 26:467-471 1981

The appearance of target cells (TC) for Abelson murine leukemia virus (A-MuLV) was studied during ontogeny by measuring the frequency of TC in fetal liver at various times during gestation. Susceptibility to A-MuLV was measured using the quantitative agar assay. The frequency of susceptible cells was greatest late in gestation, with the max number of transformed foci in 18-19-day livers. Steadily decreasing numbers of foci were found at earlier times. No foci were found in 11-or 12-day livers. The number of foci in the liver dropped after birth. TC could be detected in bone marrow after birth. Infection of mixed fetal liver/adult marrow cultures indicated that failure to detect TC in early stages was due to a lack of TC, rather than to factors suppressing transformation. Transformed cells were lymphoid cells with large nuclei and one or more nucleoli. Many of the cells from adult bone marrow carried Ig and terminal deoxynucleotidyl transferase (TdT). Neonatal liver cells also carried Ig and TdT. Late fetal liver cells carried Ig, but not TdT. Early fetal liver cells carried TdT, but only reduced Ig. Changes in TdT and Ig expression apparently reflect shifts in the TC population during ontogeny. (24 Refs)

10. CHARACTERIZATION OF HEMATOPOIETIC TARGET CELLS OF DEFECTIVE AVIAN LEUKEMIA VIRUSES BY VELOCITY SEDIMENTATION AND DENSITY GRADIENT CENTRIFUGATION ANALYSES.

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Haematol Blood Transfus; 26:417-423 1981

The hematopoietic target cells of replication-defective viruses (DLV) were characterized according to physical parameters: sedimentation velocity at unit gravity (as a measure of relative size) and centrifugation in Percoll density gradients (to determine relative buoyant density). Included is a comparison of the DLV target cells to the normal granulocyte/macrophage colony-forming cells (CFU-C) which develop together with the DLV-transformed cells under the specified culture conditions. Results are discussed in relation to three categories according to the phenotype of differentiation expressed: AEV-type viruses - erythroblasts; MC29-viruses - macrophages; and AMV type strains - myeloblast-like transformed cells. Results show that in general target cells for all three DLV types were most abundant in fractions consisting mainly of blast-like, immature bone marrow cells. The target cells are similar to each other with respect to size and density. In comparison to RBC, granulocytes, and CFU-C cells they are relatively large; they are much lighter than RBC and granulocytes. Together with earlier results, results suggest that DLV target cells are immature but already committed to the erythroid or myeloid lineages and upon tra nsformation DLVs block differentiation of their target cells. Data concerning the relationship between normal macrophage/granulocyte colony forming cells and the target cells of MC29 and AMC are incomplete but suggest they are not identical. (14 Refs)

11. STUDIES OF THE ASSOCIATION OF LEUKEMOGENIC AND ONCOGENIC PROPERTIES IN AVIAN LEUKEMIA VIRUSES.

Loliger HC, Von dem Hagen D, Hartmann W
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Haematol Blood Transfus; 26:452-454 1981

Induction of leukocytic and nonleukocytic neoplasias by avian myeloblastosis virus (AMV) and Marek's disease herpes virus (MDHV) was studied in chickens of Leghorn line R (cell types c/O, c/A, and c/AB), Leghorn line M (cell types c/O and c/AB), Leghorn line G (cell type c/B), dysgammaglobulinemic line UM (cell type c/O), and SPAFAS line (cell type c/O). AMV produced leukemia and nephroblastomas in all lines with homozygous cell types c/A, c/B, and c/O, but not c/AB. MDHV induced lymphoid cell reticulosis, but no leukosis, nephroblastomas, or osteosarcomas. Pretumorous lesions of the kidney appeared in 3-wk-old chickens; gross lesions with clinical symptoms appeared between 56 and 112 days after infection, with most appearing after 70 days. Osteopetrosis and osteosarcomas occurred most often in M, UM, and SPAFAS lines. AMV infection was evident in susceptible R, M. and G chickens within 2-5 wk of infection. UM chickens showed aplastic anemia with medullar fibrosis at 12-15 days, followed by stem cell leukemia. SPAFAS chickens showed erythroblastosis first, followed by stem cell leukemia and later by nephroblastomas. The more intense the early hemoblastic disorder was, the lower the chance of development of nonleukocytic neoplasms. (5 Refs)

12. REGULATOR-DEPENDENT HAEMPOIESIS AND ITS POSSIBLE RELEVANCE TO LEUKEMOGENESIS.

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Haematol Blood Transfus; 26:272-275 1981

The regulation of stem cell proliferation and differentiation and the effects of a variety of RNA C-type leukemia viruses on in vitro hemopoiesis were investigated. Treatment with leukemogens may result in direct transformation or in alterations in the level of the various regulatory molecules. The cell lines produced in long-term cultures can be used as a model for further transformation studies. (19 Refs)

13. FELINE LEUKEMIA VIRUS NONPRODUCER LYMPHOSARCOMAS OF CATS AS A MODEL FOR THE ETIOLOGY OF HUMAN LEUKEMIAS.

Hardy WD, McClelland AJ, Zuckerman EE, Snyder HW, MacEwen EG, Francis D, Essex M
No affiliation given
Haematol Blood Transfus; 26:492-494 1981

Immunological and epidemiological studies of feline lymphosarcoma (LSA) are summarized. Immunofluorescent antibody assay, immunodiffusion, tissue culture isolation, and radioimmunoassay were used to test 507 casts with LSA for feline leukemia virus (FeLV). FeLV-positive LSA was found in 360 cats; the remaining 147 had nonproducer (NP) LSA. No FeLV proteins or infectious viruses were detected in NP LSA. However, the FeLV-induced tumor specific oncovirus-associated cell membrane antigen was detected on the surface of both NP and FeLV positive LSA cells. Of 1,612 FeLV-exposed and -unexposed cats observed for development of LSA, 0/1,074 unexposed cats (observed av 3 yr/cat) developed LSA; 149/538 exposed cats (observed av 4.4 yr/cat) were persistently infected. LSA developed in 41 cats, 30 FeLV positive and 11 NP LSA. Difference in rate of NP LSA in FeLV-exposed and -unexposed cats was significant (p less than 0.001). FeLV appears to be the etiologic agent of feline LSA regardless of FeLV status. Mechanisms by which RNA- and DNA-containing viruses induce tumors are discussed. Feline NP LSA could be a useful model for elucidating mechanisms of oncovirus transformation. (12 Refs)

14. RECEPTOR MEDIATED MURINE LEUKEMOGENESIS: MONOCLONAL ANTIBODY INDUCED LYMPHOMA CELL GROWTH ARREST.

McGrath MS, Jerabek L, Pillemer E, Steinberg RA, Weissman IL
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Haematol Blood Transfus; 26:360-364 1981

A receptor-mediated leukemogenesis hypothesis that T lymphocytes are clones of T cells bearing mitogen-linked surface receptors specific for the envelope determinants of the inducing murine leukemia virus was tested. Experiments examined the central postulate that continued leukemic proliferation is the result of continued antigenic stimulation of T lymphomas. Monoclonal antibody reagents to leukemia cell surface determinants were raised; the effect of these antibodies was tested on leukemic cell proliferation in vitro and on specific virus binding to the cells. Several antibodies which inhibited lymphoma cell proliferation in vitro were found. Evidence is presented that inhibition may be due to a blockade in virus binding to these cells. (17 Refs)

15. INDUCTION OF LYMPHOSARCOMA IN SHEEP BY BOVINE LEUKEMIA VIRUS.

Kenyon SJ, Ferrer JF, McFeely RA, Graves DC
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JNCI; 67(5):1157-1163 1981

Newborn sheep inoculated with phytohemagglutinin (PHA)-treated short-term cultures of lymphocytes from cattle infected with bovine leukemia virus (BLV) or with a BLV-infected long-term culture of bovine leukemic lymphocytes became persistently infected with BLV. Fifty percent or more of the sheep died with histologically confirmed lymphosarcomas. Cytogenetic studies of representative cases demonstrated that the tumors did not result from the progressive growth of neoplastic lymphocytes in the inoculum but rather from the neoplastic transformation of the recipient's lymphoid cells. Neither BLV infection nor lymphosarcoma was observed in control uninoculated sheep or in sheep given injections of PHA-treated cultures of lymphocytes from BLV-free cows. The virus recovered from the tumorous sheep was indistinguishable from BLV morphologically, antigenically, and biologically, and its reverse transcriptase had the same cation preference and immunologic properties as the BLV enzyme. Persistent BLV infection and lymphosarcoma were also observed in a group of sheep inoculated neonatally with BLV-containing cell-free culture supernatants. These results extend previous observations on the high susceptibility of sheep to BLV infection and provide definitive evidence that BLV is a tumor-inducing virus. (Author abstract) (33 Refs)

16. REGULATION OF HUMAN T-CELL PROLIFERATION: T-CELL GROWTH FACTOR AND ISOLATION OF A NEW CLASS OF TYPE-C RETROVIRUSES FROM HUMAN T-CELLS.

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NCI, Bethesda, MD, 20014
Haematol Blood Transfus; 26:502-514 1981

Recent results with human T-cell growth factor (TCGF), the various T cell systems, and the isolation of a new type-C retrovirus released from growing T-cells from some of these T-cell neoplasias are summarized. Unlike normal T-cells, neoplastic mature T-cells respond directly to TCGF without prior lectin or antigen in vitro activation. Transformed T-cell lines exhibit phenotypic characteristics consistent with the neoplastic cells of their disease of origin. A new retrovirus, human T-cell lymphoma-leukemia virus (HTLV) was isolated from fresh and cultured cells from two patients, each with a variant of a cutaneous T-cell lymphoma. Further studies showed that HTLV was not significantly related to any known animal retrovirus, is not an endogenous (genetically transmitted) virus of man, and at present is only associated with fresh or cultured T-cells from patients with the T-cell neoplasia. The results suggest that HTLV infected some mature T-cells of some people and may be involved in some neoplasias involving these cells. (33 Refs)

17. TRANSFORMING GROWTH FACTORS - CHARACTERIZATION OF TWO CLASSES OF FACTORS FROM BOTH NEOPLASTIC AND NON-NEOPLASTIC TISSUES (MEETING ABSTRACT).

Roberts AB, Anzano MA, Frolik CA, Sporn MB
National Cancer Institute, Bethesda, MD, 20205
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

We report here that transforming growth factors (TGF's) from several sources fractionated by chromatography on Bio-Gel P-30 can be separated into two distinct classes of growth factors following high pressure liquid chromatography on microBondapak C18 columns using gradients of acetonitrile and water containing 0.1% trifluoroacetic acid. One class has properties similar to those originally described for sarcoma growth factors. This class of TGF's elutes from microBondapak C18 earlier than epidermal growth factor (EGF), used as a marker, and is characterized by competition with EGF for membrane receptor sites and by its ability to induce colony formation in soft agar. The second class of TGF's elutes from microBondapak C18 later than the EGF marker and is characterized by its ability to enhance EGF binding in a radioreceptor assay, and an apparent requirement for EGF for activity in the soft agar growth assay. The low intrinsic colony-forming activity of this new class of TGF's is amplified several hundred fold by the addition of 2 ng/ml EGF, which by itself also has only weak colony-forming activity. Assayed in the presence of EGF, the new class of EGF-dependent TGF's from murine sarcoma virus-transformed mouse 3T3 cells represents over 80% of the total colony-forming units of the 6-12K region of the Bio-Gel P-30 chromatogram. The observation that EGF acts synergistically with certain TGF's places new emphasis on the role of EGF as a controlling factor in neoplastic progression and possibly other proliferative states such as wound healing. (1 Ref)

18. TUMOR PROMOTERS ALTER GENE EXPRESSION AND PROTEIN PHOSPHORYLATION IN AVIAN CELLS IN CULTURE.

Laszlo A, Radke K, Chin S, Bissell MJ
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Proc Natl Acad Sci USA; 78(10):6241-6245 1981

We have investigated the effect of 12-O-tetradecanoylphorbol 13-acetate (TPA) on the synthesis and modification of polypeptides in normal avian cells and cells infected by wild-type and temperature-sensitive Rous sarcoma virus (RSV). Using two-dimensional gel electrophoresis, we have detected alterations in both the abundance of cellular polypeptides and in their phosphorylation that seem unique to TPA treatment. However, the state of phosphorylation of the major putative substrate for the action of the src gene-associated protein kinase, the 34-to 36-kilodalton protein, was not altered. Moreover, examination of the phosphorylated amino acid content of total cellular phosphoproteins revealed that the response to TPA was not associated with detectable increases in their phosphotyrosine content. These results make it unlikely that TPA acts by the activation of the phosphorylating activity of the cellular proto-src gene or by the activation of other cellular phosphotyrosine-specific kinases. We have shown previously that temperature-sensitive RSV-infected cells at nonpermissive temperature demonstrate an increased sensitivity to TPA treatment. Our present results indicate that this is not due to reactivation of the phosphorylating activity of the defective src gene product or to its leakiness, and they lend support to the notion of multistep viral carcinogenesis. (Author abstract) (29 Refs)

19. SYSTEMS FOR DETECTING TUMOR-PROMOTERS (MEETING ABSTRACT).

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In Vitro; 17(3):236 1981

The role of tumor viruses in the etiology of human cancer has remained obscure. Nevertheless, not only do virus-infected cells provide a model for studying malignancy in animals, but they also provide a sensitive system for detection of tumor promoters. Fibroblasts prepared from body wall of 10-day-old chich embryo or from more differentiated 16-day-old chick tendon cells respond to tumor promoters by manifesting many of the 'transformation parameters' characteristic of retrovirus-infected cells in culture. Cells infected with temperature sensitive (ts) mutants of Rous sarcoma virus (RSV) at the non-permissive temperature have an exaggerated response and become very similar to cells transformed by wild type RSV. These cells have proven extremely valuable in detecting promoter-like activity from various plants. Additionally, we now have shown that alterations in 2-dimensional protein patterns of secreted proteins in the medium are an extremely sensitive means of detecting the action of tumor promoters, viral infection and other environmental carcinogens. The assay is also useful for detecting synergism between viruses and other carcinogens where the virus could act as the initiator or the promoter or both. (1 Ref)

20. CHEMICAL-VIRAL CO-CARCINOGENESIS IN VITRO USING CLONED MAMMARY EPITHELIAL CELLS AND MOUSE MAMMARY TUMOR VIRUS (MEETING ABSTRACT).

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In Vitro; 17(3):236 1981

We have evaluated the effect of mouse mammary tumor virus (MMTV) and 7,12-dimethylbenz(a)anthracene (DMBA), either alone or in combination, on mammary epithelial cells in vitro. A single-cell clone (clone 2), was derived from the normal mouse mammary gland cell line, C57MG, and was shown to be of murine origin by karyotyping, isoenzyme analyses, and by immunofluorescence using species-specific antisera. This clone failed to induce tumors in syngeneic or athymic (nude) mice. The epithelial origin of the cells was demonstrated by the presence of desmosomes, tonofibrils and secretory granules. Clone 2 cells were infected with MMTV host-range variant MMTV (RIII) vp4, and both infected and mock-infected cultures were treated with DMBA. Cultures treated with both virus and carcinogen exhibited morphological changes and a slight increase in ability to grow in soft agar after 5 to 7 subcultures. The most striking alteration in the phenotype of cells exposed to the combination of MMTV and DMBA, however, was an increase in their tumorigenic potential in athymic mice. Cultures treated with virus alone or DMBA alone did not show an in crease in tumorigenicity. This cell-culture model system now permits the study of the interaction of chemicals and MMTV in the initiation and promotion of mammary cell transformation. (no Refs)

21. CHROMOSOMAL ALTERATIONS IN THE COURSE OF VIRAL LEUKEMOGENESIS IN THE RAT.

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Cancer Genet Cytogenet; 4(2):143-155 1981

A cytogenetic study of 35 primary thymic lymphomas induced in rats by the Gross leukemia virus revealed the presence of widespread aneuploidies, ranging from cells with 35 chromosomes or less to triploid and tetraploid cells. Analysis by G banding revealed that chromosomes No 1, 2, 9, 12, 18-20, X in females, and Y in males were lost preferentially; unidentified marker chromosomes of various morphology and length were present in a high percentage of aneuploid mitoses. Similar alterations were observed in preleukemic thymi from rats sacrificed 30 days after virus injection, when clinical or histologic signs of the disease had not yet appeared. In rats that were sacrificed 7 or 15 days after virus injection, chromosomal anomalies were much more limited, although significantly more abundant than in the controls. Rats that were free of tumor at 130-160 days after virus injection showed a regression of the chromosomal anomalies, suggesting that these are not irreversible and are not necessarily followed by the development of a lymphoma. (Author abstract) (31 Refs)

22. TROPOMYOSIN IS DECREASED IN TRANSFORMED CELLS.

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Proc Natl Acad Sci USA; 78(9,part2):5633-5637 1981

The steady-state level and synthesis of a pair of polypeptides of Mr 33,000 and 35,000 in chicken embryo fibroblasts (CEF) transformed by Rous sarcoma virus (RSV) are significantly decreased relative to normal CEF; however, the decrease is more pronounced in the case of the Mr 35,000 polypeptide. These polypeptides have been identified as the alpha and beta subunits of CEF tropomyosin by selective staining with tropomyosin antibody, two-dimensional gel electrophoresis, partial peptide analysis, and solubility properties. The decrease in tropomyosin is shown to be a transformation-specific phenomenon in that it does not occur after infection with a virus deleted in src sequences. Decreased synthesis of tropomyosin is also observed in quail cells transformed by MC29 (a retrovirus with a different onc gene than that in RSV) and also in chemically transformed quail cells. The decrease in tropomyosin is probably not a direct result of the disruption of the microfilament system in transformed cells because disruption of the microfilament system with trypsin or cytochalasin B in normal CEF does not lead to a decrease in tropomyosin synthesis. A decrease in tropomyosin in CEF after transformation may be a result of a pleiotropic effect that results in the transcriptional inactivation not only of the tropomyosin gene but also of the fibronectin and procollagen genes described by others. (Author abstract) (34 Refs)

23. MECHANISMS OF KIRSTEN MURINE SARCOMA VIRUS TRANSFORMATION-INDUCED CHANGES IN THE COLLAGEN PHENOTYPE AND SYNTHETIC RATE OF BALB 3T3 CELLS.

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Proc Natl Acad Sci USA; 78(10):6028-6032 1981

Specific viral transformation rather than cell selection can explain the previously observed increase in the proportion of Type III procollagen compared to Type I procollagen in BALB 3T3 cells transformed by Kirsten murine sarcoma virus (Ki-MSV). Two subclones of BALB 3T3 A31 were productively infected with a temperature-sensitive Ki-MSV in the presence of helper murine leukemia virus (MLV), resulting in virtually complete transformation of cultures and eliminating selection of transformed foci. Analysis of radioactive collagen, derived from procollagen by pepsin treatment, showed that both of the tsKi-MSV/MLV-transformed subclones contained a four-fold greater proportion of Type III procollagen than did control MLV-infected cultures. A nonproducer derivative exhibited an even greater change (10-fold), indicating that viral replication was irrelevant. After 48 hr at a nonpermissive temperature, tsKi-MSV-transformed cells retained a high proportion of Type III procollagen, suggesting that either this change is not induced by src protein or else there is a slowly reversible or irreversible step involved. Alternatively, Type III procollagen mRNA may be long lived. In contrast, the relative rate of procollagen synthesis in transformed cells was clearly regulated by src protein. Translation of mRNA from cells preincubated at permissive or nonpermissive temperatures revealed that the decreased relative rate can be explained by a simultaneous small decrease in the level of procollagen mRNA and a large increase in mRNA for noncollagen proteins. (Author abstract) (36 Refs)

24. TRANSPORT OF D-GLUCOSE BY MEMBRANE VESICLES FROM NORMAL AND AVIAN SARCOMA VIRUS-TRANSFORMED CHICKEN EMBRYO FIBROBLASTS.

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Proc Natl Acad Sci USA; 78(9,part2):5358-5361 1981

Transport of D-glucose was examined in membrane vesicles from normal and avian sarcoma virus (ASV)-transformed chicken embryo fibroblasts. The initial rates of D-glucose transport were found to be 3-to 5-fold higher for vesicles from glucose-starved normal cells and ASV-transformed cells when compared with transport rates for vesicles from normal cells and serum-starved normal cells. Cytochalasin B, phloretin, and diethylstilbestrol inhibited the initial rate of transport in all types of vesicles, and 2-deoxyglucose, 3-O-methylglucose, and galactose were competitive inhibitors. At D-glucose concentrations between 0.25 and 5 mM, vesicles from normal and ASV-transformed cells displayed saturation kinetics with a Km value of 5 mM for both types of vesicles, with transformed cell vesicles showing a 3-fold increase in Vmax compared with normal cell vesicles. At D-glucose concentrations between 5 and 25 mM the initial rate of D-glucose transport was proportional to D-glucose concentration. The vesicles also showed an inhibitor-sensitive efflux at rates similar to those observed for influx. (Author abstract) (22 Refs)

25. DEXAMETHASONE EFFECT ON THE GROWTH RATE, THE PLASMINOGEN ACTIVATOR, AND THE MMTV DEPENDENT DNA POLYMERASE IN A MOUSE MAMMARY TUMOR CELL LINE.

Failly-Crepin C, Fromont S, Crepin M
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Biochem Biophys Res Commun; 102(1):22-29 1981

The effect of dexamethasone (DMS) was studied in cultured cells of murine mammary gland carcinoma (GR cells). DMS caused inhibition of exponential growth but not overall protein synthesis. Treatment with DMS resulted in significant inhibition of extra- and intracellular plasminogen activator. Reverse transcriptase associated with secreted murine mammary tumor virus particles was strongly stimulated. (20 Refs)

26. PLASMINOGEN ACTIVATOR: ANALYSIS OF ENZYME INDUCTION BY ULTRAVIOLET IRRADIATION MAPPING.

Miskin R, Reich E, Dixon K
Biochemistry Dept., Weizman Inst. Science, Rehovot, Israel
Mol Cell Biol; 1(10):884-890 1981

The UV sensitivity of plasminogen activator (PA) synthesis in normal and ts68 sarcoma virus-transformed chick embryo fibroblasts (CEF) was measured. The apparent size of the transcription units required for PA induction was examined using ribosomal RNA (rRNA) synthesis as a standard. PA induction by the tumor-promoting agent phorbol myristate acetate (PMA) in CEF was markedly inhibited at UV fluences greater than 300 ergs/square mm (mm2); at 500 ergs/mm2, intracellular PA was only slightly higher than in cultures receiving no PMA. When the PA levels in the irradiation PMA-treated cultures were corrected for unirradiated control levels, the reduction in PA induction was an exponential function of UV fluence. The value for the UV sensitivity of PA induction by PMA was converted to a target size of approx 6,600 base pairs. When PA values in transformed, PMA-treated cultures were corrected for base-line enzyme content of comparable cultures not exposed to PMA, an exponential decline was seen in PMA inducibility as a function of UV fluence. The results suggested that PA induction by PMA proceeds either by identical pathways in both transformed and normal CEF or at least by pathways that are indistinguishable on the basis of UV sensitivity. Although the level of the retinoate (RT) induction was appreciably lower than that produced by PMA and the precision of the enzyme assay reduced, RT induction was found to be significantly less UV-sensitive than that of PMA. An exponential decline in overall protein synthesis was observed as a function of UV fluence, but the slope showed that this process was much more UV resistant than either PMA- or RT-induced PA synthesis. Hence, any UV-induced damage to the cellular protein synthesizing equipment cannot account for the much larger fractional decrease seen with drug-stimulated PA induction. (30 Refs)

27. COMPARISON OF CAMP-DEPENDENT PROTEIN KINASE IN NORMAL AND ROUS SARCOMA VIRUS TRANSFORMED CHICK EMBRYO FIBROBLASTS.

Kudlow JE, Watson RK, Gill GN
Dept. Medicine, Div. Endocrinology, Univ. California, San Diego, Sch. Medicine, La Jolla, Ca, 92093
J Cyclic Nucleotide Res; 7(3):151-159 1981

Chicken embryo fibroblasts (CEF) were transformed with Schmidt-Ruppin Subgroup D Rous sarcoma virus (RSV). The activity of cyclic AMP (cAMP) dependent protein kinase (A kinase) in transformed cells was compared with th in normal cells. Two A kinase regulatory subunits from chicken skeletal muscle, both specific for cAMP, were characterized by photoaffinity labeling. Mol wt of the units were 45,000 and 42,000 Mr, about 4-5,000 daltons smaller than corresponding mammalian subunits. A single isoenzyme corresponding to the smaller subunit was found in equal quantities in normal and transformed CEF. Total cAMP binding and total A kinase activity were the same in normal and transformed CEF. The apparent Km for activation of A kinase by cAMP was 35 nanoM for each. Apparently RSV does not directly affect the amount or activity of cAMP-dependent A kinase. (31 Refs)

28. LDHK, A UNIQUELY REGULATED CRYPTIC LACTATE DEHYDROGENASE ASSOCIATED WITH TRANSFORMATION BY THE KIRSTEN SARCOMA VIRUS.

Anderson GR, Kovacik WP, Marotti KR
Dept. Cell and Tumor Biology, Roswell Park Memorial Inst., Buffalo, NY, 14263
J Biol Chem; 256(20):10583-10591 1981

A novel isozyme of lactate dehydrogenase is detected in various cells transformed by the Kirsten murine sarcoma virus (KiMSV). This isozyme, designated LDHk, is strongly inhibited by physiological concentrations of oxyen, in an apparently cooperative fashion. LDHk is inhibited by guanosine triphosphate and related compounds, in an noncompetitive fashion. LDHk is found with both 35,000-and 22,000-dalton subunits, although these probably cleave from a 57,000-dalton precursor. In studies utilizing a temperature-sensitive transforming gene mutant of the Kirsten sarcoma virus, we find in vivo expression of LDHk is also temperature-sensitive. In studies using either crude cell-free extracts or purified LDHk, we find the enzyme from cells infected with a temperature-sensitive transforming gene mutant of KiMSV is thermolabile relative to that from wild type KiMSV-infected cells. (Author abstract) (34 Refs)

29. ELECTRON-MICROSCOPIC IMMUNOCYTOCHEMICAL AND FUNCTIONAL INVESTIGATIONS OF NORMAL AND LEUKEMIA VIRUS INFECTED BONE MARROW MONONUCLEAR CELLS (MEETING ABSTRACT).

Butenko ZA, Zak KP, Komissarenko SV
Department of the Molecular Mechanisms Cancero- and, Leukemogenesis R.E. Kavetsky Institute Oncology Problems, Academy Science of, Ukraine Kiev, USSR
Eighth European Congress of Pathology, August 30-September 4, 1981, Helsinki, Finland. The Congress 92 pp., 1981.

Ultrastructure of different types of bone marrow mononuclear cells in normal and Rauscher leukemia virus infected BALB/c mice was studied. Using modern techniques of electron-microscopic immunocytochemistry including PAP method mononuclear cells bearing membrane immunoglobulins and other antigens were detected (Thy 1.1., Thy 1.2., brain associated antigens). Bone marrow lymphocytes and lymphocyte-like mononuclear cells with different colony-forming ability were studied as such and fractionated in density gradients of high mol wt substances in vivo and in vitro. The functional and submicroscopic characteristics of different bone marrow immunoglobulin-bearing lymphocytes and hemopoietic stem cells of normal and Rauscher leukemia virus infected are presented in detail. (no Refs)

30. STUDIES IN VITRO ON THE INDUCTIVE ACTION OF TUMOUR TISSUES ON THE ECTODERM OF CHICK BLASTODERM.

Zhang J
Dept. Cell Biology, Cancer Inst., Chinese Acad. Medical Sciences, Beijing, People's Republic of China
Acta Anat Sin; 12(2):192-196 1981

The ability of tumor tissues in inducing cell proliferation and cell differentiation in the ectoderm of chick blastoderm is described. Both fresh tumor tissues and those treated with 70% alcohol were used. Tumors used included Rous sarcoma, rat Walker mammary carcinoma, murine spindle cell sarcoma, murine sarcoma 180, and human esophageal carcinoma (ECA-109). Results showed that only fresh tissues from sarcoma 180 and alcohol-treated tissues from spindle cell sarcoma were able in inducing neural formation in the ectoderm of chick blastoderm. (19 Refs) (In CHI)

31. PERICELLULAR MATRIX OF VIRUS-TRANSFORMED MOUSE EPITHELIAL CELLS (MEETING ABSTRACT).

Keski-Oja J
Department of Virology, University of Helsinki, SF-00290 Helsinki 29, Finland
Eighth European Congress of Pathology, August 30-September 4, 1981, Helsinki, Finland. The Congress 92 pp., 1981.

Mouse embryo epithelial cells, MMC-E were transformed with Moloney murine sarcoma virus (MSV) or with ecotropic murine leukemia virus (C3H/MuLV). Transformed cell colonies, isolated using soft agar techniques were analyzed for their production of connective tissue glycoproteins. The nontransformed, MSV-transformed and MuLV-transformed cells produced fibronectin, laminin, type I collagen and small amounts of type III collagen as shown by immunofluorescence analysis of their pericellular matrices. The MuLV- and MSV- transformed cells produced enhanced amounts of fibronectin into their growth media as shown by metabolic labeling and polypeptide analysis. Nontransformed MMC-E cells mainly produced type I procollagen. A significant increase in the glycoprotein production was seen by the MuLV-transformed cells, whereas small changes in the collagen production were apparent after MSV-transformation. MuLV-transformed cells produced enhanced amounts of type I collagen and also some type IV collagen. The ratio of the procollagen type I chains in the matrix was significantly altered in the transformed cells indicating that type I procollagen is mainly deposited in their pericellular matrix as alpha 1 (I)-trimer. Unlike virus-transformed fibroblastic cells these transformed epithelial cells deposited and retained connective tissue glycoproteins in their matrices. The ability of virus-transformed epithelial cells to retain pericellular matrices is a major difference between them and virus-transformed fibroblastic cells in culture. (1 Ref)

32. CELLULAR TRANSFORMATION BY BOVINE LEUKEMIA VIRUS (MEETING ABSTRACT).

Amborski GF, Shane BS, Parker S, Butler D
Department of Veterinary Science, Louisiana State University, Baton Rouge, LA, 70803
In Vitro; 17(3):216 1981

Bovine leukemia virus (BLV) transformed cell lines as judged by morphological appearance, growth in reduced serum concentrations and foci formation in soft agar. Infected fetal lamb kidney cells (FLK-BLV) demonstrated foci in monolayer cultures and growth curves showed cellular multiplication in media supplemented with 2, 5 and 10% serum but not with 1%. Less than 1% of the cells grew as colonies in soft agar. Infected bat lung cells (BtLu-BLV) had less discrete foci in monolayer culture, showed similar growth patterns to FLK-BLV with varying serum concentrations but over 90% of the cells grew in soft agar. Although BtLu-BLV cells appeared more highly transformed, the amount of 3H-virus produced by both cell lines appeared similar. The exposure of both cell lines to a mutagen (5-iodo-2-deoxyuridine) did not appear to change the growth patterns in soft agar, but the level of BLV produced by both cell lines increased. (no Refs)

33. EFFECT OF MURINE LEUKEMIA VIRUSES (MULVS) ON WEHI-3 CONDITIONED MEDIUM-DEPENDENT HEMATOPOIETIC PROGENITOR CELL LINES (MEETING ABSTRACT).

Greenberger JS, Sakakeeny MA, Novak T, Hoffman N
Joint Center for Radiation Therapy, Department of Radiation Therapy, Harvard Medical School, Boston, MA, 02115
In Vitro; 17(3):217 1981

Nonadherent cells removed from corticosteroid-supplemented continuous bone marrow cultures of some mouse strains generate permanent suspension cell lines in conditioned medium (CM) from WEHI-3 mouse myelomonocytic leukemia cells. The growth factor(s) is retained after dialysis (D) of CM against distilled water and concentration five-fold by Amicon PM-10 filtration. Cloned cell lines from C3H/HeJ, C57BL/6J, and CD-1 Swiss mouse marrow cultures infected with Moloney or Rauscher (R), MuLV, or R-MuLV pseudotype viruses of Friend spleen focus-forming virus (SFFV) or Kirsten murine sarcoma virus (KiMSV) showed no alteration of in vitro doubling x or saturation density at 31 C. Each uninfected or infected line required a minimum of 10% WEHI-3 DCM. Cell lines releasing SFFV or KiMSV but not helper viruses alone produced leukemia in vivo. Each line differentiated to mature neutrophilic granulocytes in diffusion chambers in irradiated mice or in purified bone marrow stromal cultures. Some contained 0.05 to 13% toluidine-blue positive basophil-mast cells. MuLV infection of WEHI-3 DCM-dependent granulocyte progenitor cell lines does not alter several growth properties in vitro. (no Refs)

34. VIRAL MECHANISMS OF CARCINOGENESIS (MEETING ABSTRACT).

Weiss RA
Chester Beatty Research Institute, Institute of Cancer Research, Fulham Road, London SW3 6JB, England
Symposium on Host Factors in Human Carcinogenesis, June 8-11, 1981, Cape Sunion, Greece International Agency for Research on Cancer; 1981

Tumor virus genomes may be regarded as transposable genetic elements. By integrating into host cell chromosomal DNA they may cause mutations and chromosomal rearrangements that predispose to cancer. However, there is growing evidence that several strains of DNA and RNA tumor viruses carry genes that encode 'transforming' proteins. The transforming proteins of several oncogenic viruses function as protein kinases. Some of the viral 'oncogenes' are similar to cellular genes, and their normal counterparts may play roles in regulated cell differentiation and proliferation. The origin, nature and functions of these proteins will be reviewed. (no Refs)

35. EXPRESSION OF VIRAL GENES IN TRANSFORMED CELLS.

Ratovitskii EA
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Usp Sovrem Biol; 92(1):3-18 1981

Experimental data on the expression and integration of viral genes in the permissive and nonpermissive cells and on the role of viral genes in transformation of target cells are reviewed. Numerous in vitro and in vivo studies showed that the genome of host cells can control an expression of oncornavirus genes at transcription, transport of messenger RNA from the nucleus into cytoplasm, and translation stages. Viral genes were shown to stimulate globin synthesis and to inhibit collagen synthesis in chick fibroblasts transformed with Rous sarcoma virus. It was emphasized that further research would clarify whether the product of src gene affects directly expression of cellular genes or whether the exogenous provirus sequences only initiate the endogenous 'cancer' genes. (202 Refs) (In RUS)

VIRUS REPLICATION AND EXPRESSION

36. EXPRESSION OF CELL SURFACE FRIEND VIRUS GP70 DOES NOT BLOCK REINFECTION BY ECOTROPIC MURINE LEUKEMIA VIRUSES.

Chesebro B, Collins JK, Wehrly K, Nishio J, Cloyd M
U.S. Dept. Health and Human Services, Public Health Service, NIH, Natl. Inst. Allergy and Infection Disease, Rocky Mountain Lab., Hamilton, MT, 59840
Virology; 115(1):125-129 1981

The effect of cell surface gp70 expression on reinfection by murine leukemia virus was studied in Friend virus (FV)-induced erythroleukemia cell clones. A clone (2C) which released gp70-positive infectious virions and expressed large amounts of cell surface ecotropic FV gp70 was not superinfectable by ecotropic viruses, whereas another clone (7C) which expressed similar amounts of cell surface FV gp70 but released gp70-deficient virions showed no resistance to superinfection. The lack of interference to superinfection of 7C cells suggested that newly budded gp70-positive virions, rather than cell surface gp70 molecules, were responsible for the interference to superinfection seen in 2C cells which released infectious virus. (Author abstract) (19 Refs)

37. 5-AZACYTIDINE INDUCTION OF MOUSE ENDOGENOUS TYPE C VIRUS AND SUPPRESSION OF DNA METHYLATION.

Niwa O, Sugahara T
Dept. Experimental Radiology, Faculty Medicine, Kyoto Univ., 606 Kyoto, Japan
Proc Natl Acad Sci USA; 78(10):6290-6294 1981

The compound 5-Azacytidine was found to induce the expression of BALB:virus-1 and BALB:virus-2 from K-BALB cells and ecotropic endogenous virus from AKR2B cells. Efficiency of the induction was high and comparable to that by 5-bromodeoxyuridine. The level of methylcytosine in newly synthesized DNA was drastically decreased when K-BALB cells were treated with 5-azacytidine. There was an inverse relationship between the level of DNA modification and the frequency of virus expression. (Author abstract) (30 Refs)

38. INDUCTION OF ENDOGENOUS MAMMARY TUMOR VIRUS EXPRESSION DURING HORMONAL INDUCTION OF MAMMARY ADENOACANTHOMAS AND CARCINOMAS OF BALB/C FEMALE MICE.

McGrath CM, Prass WA, Maloney TM, Jones RF
Dept. Tumor Biology, Michigan Cancer Foundation, 110 East Warren Ave., Detroit, MI, 48201
JNCI; 67(4):841-852 1981

Treatment of BALB/c female mice with pituitary isografts, under conditions that established mammary hyperplasia in an anovulatory condition, enhanced mammary tumor development with prior onset of dysplastic foci in lobular parenchyma. Tumor onset began at 8 mo (mean onset time, 18 mo); the 25-mo incidence was 100%. Adenoacanthomatous tumors appeared first. Adenocarcinomas appeared only after more than 14 mo of continuous hormone stimulation. Dysplastic and neoplastic changes occurred while blood levels of the three major mammotropic hormones were physiologic. Murine mammary tumor virus (MuMTV) p28 was detected in all tumors tested, independent of time of tumor appearance or tumor type, although keratinizing cells in adenoacanthomatous tumors did not contribute to MuMTV antigen expression. MuMTV gp52 was detected in only a small fraction of cells in a few tumors. MuMTV RNA contents were above normal in all tumors tested. Neither MuMTV structural antigens nor RNA was induced in normal glands by the same hormone treatment that ultimately resulted in dysplasia and tumor formation and elevated levels of these viral markers in neoplasms. The MuMTV RNA in all hormone-induced tumors was readily distinguishable in base sequence from standard MuMTV RNA but indistinguishable from MuMTV RNA recovered from lactating mammary glands of BALB/c females carrying only endogenous MuMTV proviruses, suggesting that endogenous MuMTV RNA sequences were induced in hormone-induced neoplasms. RNA indistinguishable from MuMTV sequences present in hormone-induced primary tumors was also detected in multiple genomic equivalents in two independently derived hormone-induced premalignant alveolar hyperplasias. MuMTV p28 was detected, but gp52 was not. The same hormone stimulus that generated 100% tumors in normal glands greatly accelerated tumor development in premalignant hyperplasias but did not amplify MuMTV RNA or antigens in either hyperplasias or the tumors derived from them. B-type virions were not detected in these tissues, in either hypophyseal implant-stimulated or virgin hosts. Cell-free virions were not detected in culture. These data suggest that the replication of MuMTV induced in hormone-induced neoplasms is defective. Details of its expression suggest that if involved in events leading to tumors, its involvement is insufficient cause for those tumors. (Author abstract) (41 Refs)

39. PHENOTYPIC CHARACTERIZATION IN MICE OF THYMUS TARGET CELLS SUSCEPTIBLE TO PRODUCTIVE INFECTION BY THE RADIATION LEUKEMIA VIRUS.

Boniver J, Decleve A, Honsik C, Leiberman M, Kaplan HS
(c/o Kaplan) Cancer Biology Res. Lab., Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
JNCI; 67(5):1139-1151 1981

The spread of virus replication was studied by electron microscopy in the thymuses of inbred C57BL/Ka mice after intrathymic inoculation of the radiation leukemia virus (RadLV). The first Type C-budding virus particles appeared in scarce blast cells of the subcapsular zone. Most of these blast cells were 'X-cells,' ie, the thymus lymphoid cells most actively engaged in DNA synthesis. Virus replication spread to the entire cortical blast cell population and, from Day 7 on, to the small cortical lymphocytes. The first virus-producing cells were derived from a very few target cells (approx 0.001-0.003% of thymocytes) susceptible to RadLV infection. For determination of the phenotypes of these target cells, various thymocyte subpopulations obtained through a battery of cell separation methods were tested for their ability to support the replication of RadLV/VL3 virus in short-term culture. Most of these target cells were sensitive to the lytic effect of hydrocortisone and migrated in the fastest fraction of a 1xG sedimentation gradient, together with the majority of [3H]thymidine-incorporating blast cells. They exhibited an intermediate density and expressed H-2 and Thy 1.2 cell surface antigens, although they were not found preferentially among the high Thy 1.2 population to which most of the cortical blast cells belonged. The spread of RadLV within the thymus and the surface phenotype characteristics of target cells indicate that these cells correspond to a thymocyte subset at the earliest stage of thymic lymphopoiesis and may be transitional between the prothymocytes and the subcapsular blast cell population. (Author abstract) (47 Refs)

40. RADIATION-INDUCED MURINE LEUKEMIAS AND ENDOGENOUS RETROVIRUSES: THE TIME COURSE OF VIRAL EXPRESSION.

Erfle V, Hehlmann R, Schetters H, Schmidt J, Luz A
Gesellschaft fur Strahlen- und Umweltschaden, Ingolstadter Landstrasse 1, 8042 Neuherberg, W. Germany
Haematol Blood Transfus; 26:537-540 1981

The possible role of endogenous retroviruses in induction of radiation-induced leukemias was examined; both time course of retrovirus expression and tissue distribution of viral expression were evaluated. Pathogen-free female C57Bl/6 mice were submitted at 4 wk of age to 4 x 175 rad whole-body irradiation in weekly intervals. Irradiated and control mice were sacrificed monthly, and tissue samples taken for cocultivation with indicator cells (C3H 10T1/2 for N-tropic ecotropic virus and mink lung CCL 64 cells for xenotropic virus) and determination of viral proteins. Virus growth was tested by immunoperoxidase staining with antimurine leukemia virus, anti-p30 serum, and by the XC plaque test. Irradiation resulted in total incidence of lymphoblastic leukemia in 17/50 mice within 12 mo after treatment. Ecotropic virus (which infects mouse cells) was isolated in only 1-2 animals/mo (most during mo 6-9), and no major differences were seen between treated and control animals. Xenotropic virus (which does not infect mouse cells) was isolated in much higher frequency and most often in irradiated mice (peak period mo 5-10): rates were 45% vs 28% in controls for spleen, 21% vs 4% for thymus, and 52% vs 24% for bone marrow. Lymph node xenotropic virus yield was equally low in both groups (7%). Virus expression in leukemic animals was wi thout regular pattern. With increasing age, controls exhibited increasing antibody titers against eco- and zenotropic virus; titers in irradiated animals followed the same pattern except in the 2 mo after last treatment, when titers were markedly higher than in controls. Viral p30 protein content in all tissues studied was similar in the two groups during the observation period. Results do not indicate a major role for ecotropic viruses in development of radiation-induced murine leukemia. Induction of antiviral antibodies may be a first step toward unlimited growth. (13 Refs)

41. RETROVIRUS PARTICLE PRODUCTION IN THREE OF FOUR HUMAN TERATOCARCINOMA CELL LINES.

Lower J, Lower R, Stegmann J, Frank H, Kurth R
No affiliation given
Haematol Blood Transfus; 26:541-544 1981

Cells lines (GH, HL, Tera-1, and Tera-2) derived from human teratocarcinomas were studied for virus expression. The initial search for retrovirus particle expression in Tera-1 and Tera-2 cells by electron microscopy revealed only a single particle with an equivocal morphology of retroviruses in a Tera-1 culture. After treatment of the cultures with iododeoxyuridine, dexamethasone, and dimethylsulfoxide for 24 hr, retrovirus particles could be easily detected in 3/4 teratocarcinoma cell lines. All other human cell cultures, including choriocarcinomas, seminomas, fibroblasts, and melanomas, etc, remained virus negative even after the induction regime. The observed particles resembled C-type retroviruses but shared a unique morphologic feature with viruses found budding from the syncytiotrophoblast of human term placentas in that their core appeared adjacent to the virus envelope without the usual intermittent space seen with C-type virus particles. After induction treatment, not only a striking increase in virus production but also an alteration in cell morphology was recognizable. In the differentiated tumor cell populations, the proportion of cells producing virus-like particles as judged by electron microscopy varied from a few in HL to over 10% in Tera-1 to almost 100% in GH cultures. While in Tera-1, GH, and HL cells, human chorionic gonadotropin (HCG) production after induction was significantly increased, this hormone was not detectable in the supernatant of Tera-2 cell cultures. Induction of enhancement of virus synthesis was thus paralleled by induction of HCG production. Reverse transcriptase activity was not clearly demonstrated in these cell lines. The teratocarcinoma viruses were not shown to be infectious. (13 Refs)

42. PREVALENCE OF BOVINE LEUKEMIA VIRUS INFECTION IN FLORIDA.

Burridge MJ, Puhr DM, Hennemann JM
Dept. Preventive Medicine, Coll. Veterinary Medicine, Univ. Florida, Box J-136, Gainesville, FL, 32610
J Am Vet Med Assoc; 179(7):704-707 1981

A serologic study was undertaken to determine the prevalence of bovine leukemia virus (BLV) infection in dairy and beef cattle in Florida. Using the agar gel immunodiffusion test with a glycoprotein antigen, 47.8% of 7,768 dairy cattle and 6.7% of 4,911 beef cattle were found to have antibodies to BLV. The prevalence of BLV antibodies increased significantly (p greater than 0.0001) with increasing age. After data were adjusted for age, prevalence of BLV antibodies was significantly associated with dairy breed (p less than 0.05) but not with species (Bos taurus and B indicus) or sex. (Author abstract) (30 Refs)

43. PRODUCTION OF NONINFECTIVE VIRIONS OF ROUS SARCOMA VIRUS BY VIROGENIC HAMSTER CELLS.

Cherepantseva EA, Zakharova LG, Zakhaleva VA, Shevliagin VIa
N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR
Vopr Virusol; (4):485-488 1981

Production of noninfective virions of Rous sarcoma virus (RSV) was studied in virogenic hamster 23x cells. Electron microscope examination of the virogenic cells showed the presence of two kinds of virions of type C; the majority of the virions had a morphology similar to that of mammalian oncoviruses, and less than 10% of the virions were similar to avian oncoviruses. Virions containing the major internal protein p27 of RSV carried the surface antigenic determinants of hamster oncovirus. (17 Refs) (In RUS)

GENETICS

44. GENETICS OF SUSCEPTIBILITY TO RADIATION-INDUCED LEUKEMIA. MAPPING OF GENES INVOLVED TO CHROMOSOMES 1, 2, AND 4, AND IMPLICATIONS FOR A VIRAL ETIOLOGY IN THE DISEASE.

Meruelo D, Offer M, Flieger N
Irvington House Inst., New York Univ. Medical Center, New York, NY, 10016
J Exp Med; 154(4):1201-1211 1981

The genetics of susceptibility to radiation-induced leukemia in (A/J x B10)F2 mice were defined and the genes involved were localized. A major locus conferring resistance to fractionated irradiation (Cs-137; 180 rad/wk for 4 wk) induction of leukemia was mapped in chromosome 2 (Ril-1). Loci next to xenotropic murine leukemia virus (MuLV) envelope-related cell-surface antigens (XenCSA) on chromosome 4 (Ril-3) and Pep-3 on chromosome 1 (Ril-2) also influenced susceptibility to the leukemia. Leukemia incidence on day 250 after last irradiation was 86% and 90% in mice lacking the phenotypes Ly-6.2 or Ly-11.2, respectively, on chromosome 2. Effects related to genes linked to Ly-15.2R and Pep-3 loci were less important: the number of phenotype-nonleukemic animals 300 days after irradiation were 29% (phenotype 15.2/15.2) and 15% (Pep-3 phenotype AA). Ril-1 is located in a chromosomal site rich in thymus differentiation-specific loci; a linkage of Ril-1 and Ly-11 suggests that this region of chromosome is not silent to the inductive effects of fractionated irradiation. Tissue-specific activation of endogenous viruses may be explained by dependency on differentiation-specific steps. (40 Refs)

45. CONTINUOUS PRODUCTION OF ROUS SARCOMA VIRUS FREE OF TRANSFORMATION DEFECTIVE VIRUS IN CLONES OF ESTABLISHED RSV-TRANSFORMED QUAIL CELLS.

Marx M, Cerutti P, Hill M, Carloni G, Sergeant A, Kaczorek M
(c/o Hill) Dept. Cellular and Molecular Biology, Inst. Cancerology and Immunogenetics, Villejuif, France
Virology; 115(1):10-19 1981

Quail embryo fibroblasts were infected with a Schmidt-Ruppin strain RSV x chf recombinant virus. Virus-transformed cells were established as a permanent line and then cloned in methyl cellulose. Out of 140 clones isolated four clones were capable of indefinite growth. These clones were examined for (i) production of sarcoma and td virus particles, (ii) number of integrated virus genome equivalents, and (iii) deletions of the src gene in the provirus. We found that the clones yield about 10(6) focus-forming units of the sarcoma virus per ml of the culture medium. No td virus could be detected by plating of the virus at the endpoint dilution and no 35 S td virus RNA but only 38 S sarcoma virus RNA was found in virions. Hybridization kinetic studies indicated that three different clones contain about two virus genome equivalents, and one clone contains about four virus genome equivalents per diploid cell. Upon transfection the proviruses of different clones generated sarcoma viruses and no td viruses. Finally digestion with EcoRI restriction endonuclease released in all four clones a 1.9 x 10(6)-dalton fragment characteristic of the complete src gene, while no 0.8 x 10(6)-dalton fragment characteristic of a td provirus could be detected. We concluded that the clones of RSV-transformed quail cells contain only nondefective sarcoma proviruses and produce from these proviruses nondefective focus-forming virions in the absence of any segregant td virions. (Author abstract) (39 Refs)

46. FV-4: GENE CONTROLLING RESISTANCE TO NB-TROPIC FRIEND MURINE LEUKEMIA VIRUS. DISTRIBUTION IN WILD MICE, INTRODUCTION INTO GENETIC BACKGROUND OF BALB/C MICE, AND MAPPING OF CHROMOSOMES.

Odaka T, Ikeda H, Yoshikura H, Moriwaki K, Suzuki S
Inst. Medical Science, Minato-ku, Shirokanedai 4-6-1, Tokyo 108, Japan
JNCI; 67(5):1123-1127 1981

A gene controlling resistance to NB-tropic Friend murine leukemia virus (F-MuLV) was studied in wild mice. Mice of various subspecies were crossed with inbred BALB/c mice, and their F1 hybrids were tested for resistance to F-MuLV. Some mice of Mus musculus molossinus (Japan), M musculus castaneus (Taiwan and the Philippines), and M musculus urbanus (Sri Lanka) appeared to have the dominant resistance gene. A partially congenic strain, BALB/c-Fv-4wr (C4W), was established by the introduction of the gene Fv-4wr from a M musculus molossinus into the genetic background of BALB/c mice. [(C4W x DBA/2) x C57BL/6-Fvs] crosses revealed that Fv-4wr is located on chromosome 12 with the gene order of Fv-4w-Pre-1-Igh-1, apparently at the same site as the Fv-4. The resistance of C4W mice was indistinguishable from the Fv-4-controlled resistance of FRG mice. (Author abstract) (22 Refs)

47. GENETIC APPROACHES TOWARD ELUCIDATING THE MECHANISMS OF TYPE-C VIRUS-INDUCED LEUKEMIA.

Aaronson SA, Barbacid M, Dunn CY, Reddy EP
Lab. RNA Tumor Viruses, NCI, Bethesda, MD, 20014
Haematol Blood Transfus; 26:455-459 1981

The mechanisms of induction of leukemia by murine type-C viruses was studied in newborn NIH/Swiss mice. Inoculations of 5 x 10(4) XC pock forming units of either Rauscher (R) or Moloney (M) murine leukemia virus (MuLV) produced gross enlargement of spleen and lymph nodes as early as 10-11 wk. RMuLV produced spleen enlargement and sometimes liver and peripheral or visceral lymph node enlargement. MMuLV produced thymus enlargement in most animals, and frequently affected other lymphoid organs. MMuLV-induced tumors were of T cell origin, as indicated by presence of Thy1 antigen and absence of Fc or C3 receptors. RMuLV-induced tumors were of B cell lineage, as indicated by presence of Fc receptors and absence of Thy1 antigen. Recombinant forms between oncogenic and nononcogenic type-C viruses were produced in wild mouse embryo cells of line WM-C. These recombinants contained genetic information in varying amounts from both parental viruses and exhibited varying degrees of oncogenicity. Results indicate that target cells for transformation by RMuLV and MMuLV contain specific markers distinguishing them from other lymphoid elements. The necessity of active virus replication for tumorigenesis by murine type-C viruses is suggested. (19 Refs)

IMMUNOLOGICAL STUDIES

48. INHIBITORS OF MONOCYTE RESPONSES TO CHEMOTAXINS ARE PRESENT IN HUMAN CANCEROUS EFFUSIONS AND REACT WITH MONOCLONAL ANTIBODIES TO THE P15(E) STRUCTURAL PROTEIN OF RETROVIRUSES.

Cianciolo G, Hunter J, Silva J, Haskill JS, Snyderman R
Lab. Immune Effector Function, Duke Univ. Medical Center, Durham, NC, 27710
J Clin Invest; 68(4):831-844 1981

Individuals with cancer have previously been shown to have abnormal chemotactic responsiveness. Surgical removal of the tumor often resulted in normalization of monocyte function, which suggests that human neoplasms might inhibit monocyte chemotaxis by release of soluble mediators. We therefore examined the effects of cancerous effusions on monocyte polarization, ie, the rapid change in monocyte morphology from round to a triangular 'motile' configuration in response to chemoattractants. All 17 malignant effusions, representing 15 tumor types, inhibited monocyte polarization induced by the chemoattractant N-formyl-methionyl-leucyl-phenylalanine by 45-89% (mean 55.9 +-12.7%, p less tha n 0.01) in blinded assays. None of 17 benign effusions significantly inhibited polarization (0-15% mean 6.2 +-4.2%). Dilutions of cancerous effusions as low as 1:200 produced inhibition that was time, temperature, and dose dependent. Monocyte polarization induced by activated serum or by chemotactic lymphokine was also blocked by cancerous effusions. The inhibitory activity affected the monocyte directly, and did not destroy the chemoattractant or block the polarization of granulocytes to chemotactic factors. High pressure liquid chromatography of five cancerous fluids revealed three peaks of inhibitory activity: greater than or equal to 200,000, 46,000 +-13,000, and 21,000 +-3,000 daltons. Fractionation of noncancerous effusions revealed only small amounts of the highest mol wt inhibitory activity. The inhibitory activity in cancerous effusion was heat stable (56 C, 30 min), trypsin sensitive, and could be adsorbed by three different monoclonal antibodies reactive to P15(E), a structural component of Type C retroviruses. In contrast, six monoclonal antibodies with other specificities had no effect on the inhibitors of polarization. This study demonstrates that human cancerous effusions contain novel proteins that are potent inhibitors of monocyte function and that are recognized by antibodies reactive to the P15(E) component of retroviruses. By producing such factors tumor cells may subvert monocyte-mediated surveillance. (Author abstract) (40 Refs)

49. INHIBITION OF ANTIGEN-INDUCED T-CELL PROLIFERATION BY ANTIBODIES TO ENDOGENOUS AKR-MULV.

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Cell Immunol; 64(1):102-118 1981

Lymph node cells from BALB/c mice immunized with ovalbumin or human gamma-globulin were restimulated in vitro with these antigens and assayed for antigen-induced proliferation. The proliferative response was shown to be antigen specific and T cell dependent. A rabbit antiserum to envelope and core proteins of AKR murine leukemia virus was found to inhibit antigen-induced T-cell proliferation. The IgG fraction and F(ab')2 fragments of the antiserum were also inhibitory. The inhibition occurred after the initial step of antigen-T cell interaction and viral absorption studies showed the inhibition to be specific for anti-AKR virus antibodies. A hypothesis for the mechanism of inhibition is discussed in relation to a functional role for endogenous murine leukemia virus. (Author abstract) (36 Refs)

50. USE OF AN ELECTROIMMUNODIFFUSION METHOD ON CELLULOSE ACETATE FILMS FOR THE DETECTION OF ANTIGENICITY IN HUMAN BREAST CANCER THAT IS RELATED TO THE MAJOR CORE ANTIGEN OF MOUSE MAMMARY TUMOR VIRUS (MUMTV).

Kryukova IN, Komarova E, Zotter S, Grossmann H

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Arch Geschwulstforsch; 51(6):517-521 1981

The method developed by Abelev was used for detection of MuMTV-related antigens in tumor tissue and sera of breast cancer patients. The highly sensitive electroimmunodiffusion method on acetate films employed isotachophoresis. In 2/5 breast cancer extracts, protein fractions of about 50,000 mol wt exhibited antigenicity related to the major core antigen of MuMTV (p27). This antigenicity was not detected in the patients' sera. (18 Refs)

51. ELISA FOR THE DETECTION OF ANTIGENS CROSS-REACTING WITH PRIMATE C-TYPE VIRAL PROTEINS (P30,GP70) IN HUMAN LEUKEMIC SERA.

Hehlmann R, Schetters H, Erfle V
Institut fur Biologie, Ingolstadter Landstrasse 1, 8042 Neuherberg, W. Germany
Haematol Blood Transfus; 26:530-536 1981

The enzyme linked immunosorbent assay (ELISA) was employed in the detection and quantification of the core protein p30 of murine leukemia viruses (MuLV), the baboon endogenous virus (BaEV) and simian sarcoma virus (SSV) and the envelope glycoprotein p70 of SSV. ELISA was successfully applied in detection and quantification of p30 in tissue culture cells, tumor cells, and sera. It was also used successfully when applied to the viral glycoprotein of SSV gp70. Reactivity of gp70 was not altered by glycosidases. Proteins reacting with antibodies against p30 of BaEV and SSV were specifically detected in leukemic sera, but not, or at only very low levels, in sera from non-leukemic patients and healthy controls. Cross-reacting antigens were detected with anti-SSV p30 IgG in 15/49 leukemic sera and with anti-BaEV-p30 IgG in 19/49 leukemic sera. Antigens cross-reacting with viral envelope glycoprotein of SSV were detected in both normal and leukemic sera. In a study of the sera of 23 patients with chronic myelogenous leukemia in blast crisis, 16 were positive for one or more structures cross-reacting with SSV gp70. The fact that many of these 16 patients had a shorter survival than the non-reactors suggests a possible prognostic role for these antigens. (19 Refs)

52. A VIRAL ANTIGEN AS A MARKER FOR THE PROGNOSIS OF HUMAN BREAST CANCER (MEETING ABSTRACT).

Keydar I, Selzer G, Chaitcik S, Hareuveni M, Karby S, Hizi A
Department of Microbiology, The George S. Wise Center for Life Sciences, Tel Aviv University, Ramat Aviv, Israel
Eighth European Congress of Pathology, August 30-September 4, 1981, Helsinki, Finland. The Congress 92 pp., 1981.

The presence of an antigen immunologically related to gp52 (a 52000 dalton glycoprotein of the mouse mammary tumor virus) in human breast cancer was reported a few yr ago. The possible use of this viral related antigen as a marker for the detection of human breast cancer was studied in an Israeli population. The results obtained show that the gp52 cross-reacting antigen is detected in 58.8% of Jews originating from Europe, whereas in Oriental Jews (African-Asian origin) the percentage of positive cases is much higher (74.5%) as tested by the immunoperoxidase assay. Furthermore, a retrospective study of 104 cases of breast cancer patients in stage 2, shows clearly that if the antigen is detected at the time of biopsy one can predict an unfavorable prognosis of the disease. (no Refs)

53. CHARACTERIZATION OF ANTIGENS IN SSV NONPRODUCER CELLS.

Thiel HJ, Matthews T, Broughton E, Butchko A, Bolognesi D
Dept. Surgery, Medical Center, Duke Univ., Durham, NC, 27710
Haematol Blood Transfus; 26:520-523 1981

In an attempt to identify putative transformation specific information coded by simian sarcoma virus (SSV), goat cells nonproductively transformed by SSV (SSV-NP) were isolated and inoculated several times as live cells into the same goat. The resulting hyperimmune serum (SSV-NP serum) was reacted in radioimmunoprecipitation against different transformed and nontransformed cell lines. After labeling SSV-NP cells with 3H-glucosamine and 35S-cysteine using a 7 hr pulse followed by a 14 hr chase, the respective tissue culture supernatants were immunoprecipitated with SSV-NP serum. The SSV-NP serum reacted specifically with two different molecules in SSV-NP cells, a SSV transformation-specific glycoprotein (SSV TrS-gp) and p65, which probably represents a modified gag-precursor. (7 Refs)

54. EFFECT OF VINBLASTINE ON DISTRIBUTION OF MURINE LEUKEMIA VIRUS-DERIVED MEMBRANE-ASSOCIATED ANTIGENS.

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Proc Natl Acad Sci USA; 78(10):6266-6270 1981

The effect of vinblastine on the distribution of murine leukemia virus-derived membrane-associated antigens was examined by using the indirect immunofluorescence of 3.7% formaldehyde-fixed MJD-54 (Moloney murine leukemia virus-infected) cells. On fixed, non-drug-treated cells, p30 antigen was distributed homogeneously and diffusely over the cell membrane. When cells were incubated with 10 uM vinblastine for 1 hr before fixation, the distribution of p30 antigen was greatly changed, fluorescence now being collected into poles (cap-like formation). In contrast to this distribution pattern for p30 antigen, gp70 antigen was distributed in a micropunctate pattern on the cell surface, with or without vinblastine pretreatment. These observations indicate that the distribution patterns of p30 and gp70 membrane antigens are completely different and that they are differently controlled by cytoplasmic microtubules. In addition, because the p30 membrane antigen visualized in these studies most likely represents viral Pr65gag precursor molecules which are localized directly under and associated with the plasma membrane, these results suggest th at, under special conditions of fixation, it is possible to obtain a cap-like phenomenon for cytoplasmic (internal) membrane-oriented proteins. (Author abstract) (24 Refs)

55. TOPOGRAPHICAL ANALYSIS OF VIRAL EPITOPES USING MONOCLONAL ANTIBODIES: MECHANISM OF VIRUS NEUTRALIZATION.

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Virology; 115(1):20-32 1981

The mouse mammary tumor virus (MMTV) was used in neutralization studies with monoclonal antibodies (monoclones) to the major external glycoprotein gp52. Monoclones to MMTV gp52 showed that epitopes with different antigenic specificities were targets for virus neutralization. These epitopes were group specific (common to C3H, GR, RIII, and C3Hf MMTVs), class specific (common to C3H and GR MMTVs), and type specific (unique to C3H MMTV). Competitive antibody binding assays using a radioiodinated C3H MMTV type-specific neutralizing monoclone revealed that all the monoclones that neutralized virus infectivity also blocked the binding of the type-specific monoclone to C3H MMTV. A topographically distinct site from this determinant was found using other monoclones which did not compete for the binding of the type-specific monoclone and their epitopes did not function as targets for neutralizing antibodies. However, these non-neutralizing monoclones could neutralize virus infectivity in the presence of antimouse IgG sera. Therefore two topographically distinct sites could be identified on a single protein of the virus. One site functioned as a target for neutralization and the second site bound antibody but did not affect neutralization. The observation that virus bound to cells was no longer susceptible to neutralization by monoclones showed that neutralization affected virus prior to its binding to cell surface receptors. This result further indicated that antibody prevented virus adsorption to cells and that neutralization was mediated by steric hindrance from antibodies binding to epitopes adjacent to those determinants which functioned in virus binding to cell surface receptors. (Author abstract) (33 Refs)

56. IMMUNOLOGICAL CHARACTERIZATION OF A LOW ONCOGENIC MOUSE MAMMARY TUMOR VIRUS FROM BALB/CNIV MICE.

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J Virol; 40(1):56-64 1981

Antigenic determinants of mouse mammary tumor virus (MuMTV) from the low-mammary-tumor-incidence strain BALB/cNIV were compared by competition radioimmunoassay with those of MuMTV's isolated from several high- and low-mammary-tumor-incidence mouse strains, using rabbit hyperimmune sera against BALB/cNIV MuMTV and against MuMTV from the high-mammary-tumor-incidence strain BALB/cfC3H. Using anti-BALB/c fC3H serum in competition radioimmunoassay, BALB/cNIV MuMTV lacked antigenic determinants present on MuMTV's from the BALB/cfC3H, C3H, and GR strains. With anti-BALB/cNIV serum in competition radioimmunoassay, type-specific antigenicity was detected with BALB/cNIV MuMTV. We found class-specific antigenicities on BALB/cNIV MuMTV that were shared with RII and C3Hf MuMTV'S. BALB/cNIV MuMTV was reportedly derived from the C3Hf strain by infection of BALB/c mouse mammary tissue after transplantation into a (BALB/c x C3Hf)F1 hybrid followed by retransplantation into the BALB/c strain. However, BALB/cNIV MuMTV contained type-specific antigens not present on C3Hf MuMTV. The possible origin of these determinants is discussed. (Author abstract) (31 Refs)

57. NATURAL ANTIBODIES TO BLV GP51 ARE REACTIVE AGAINST THE CARBOHYDRATE MOIETY OF THE GLYCOPROTEIN.

Portetelle D, Bruck C, Mammerickx M, Burny A
No affiliation given
Haematol Blood Transfus; 26:498-501 1981

The antigenic site of bovine leukemia virus (BLV) gp51 exposed at the cell membrane of virus-producing cells and recognized as target by sera exhibiting strong cytolytic activity towards these cells was examined. Sera 2146 and 2152 were prepared in the rabbit by injection of BLV-infected bovine lymphocytes. Sera 67 and 82 were from cattle in the tumor phase of enzootic bovine leukosis. Serum 3162 was obtained from an animal in persistent lymphocytosis and serum 351628 was derived from an asymptomatic BLV carrier. Rabbit serum 167 was raised by injection of purified BLV gp51. Natural sera 67 and 351628 exhibited strong cytolytic activity (approx 100% and 80%, respectively) compared with rabbit serum 167 (approx 2%) at reciprocal of serum dilution = 5. Competition radioimmunoassay between bovine serum 67 and rabbit serum 2146 and solid phase radioimmunoassay indicated that (1) natural and rabbit sera react with different gp51 antigenic regions, and (2) the antigenic site recognized by natural sera is unique. Glycosidase treatment of 125I-labeled antigen followed by addition of a variety of antisera revealed the importance of the gp51 carbohydrate moiety: sera 2152, 3162, and 67 lost reactivity almost completely (from approx 70-100% to 20% or less at log reciprocal of serum dilution = 2). However, glycosidase digestion lowered max precipitability of gp51 in the presence of serum 167 by only 20%. Protease treatment of the antigen suggests that the gp51 polypeptide backbone is the target for serum 167. (4 Refs)

58. IMMUNOPROPHYLAXIS OF TRANSPLANTABLE METHYLCHOLANTHRENE-INDUCED MURINE FIBROSARCOMAS BY IMMUNIZATION WITH EMBRYO CELLS EXPRESSING ENDOGENOUS MURINE LEUKEMIA VIRUS ANTIGENS.

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Cancer Res; 41(11,part1):4499-4507 1981

We investigated the nature of a common tumor rejection antigen(s) in chemically induced murine fibrosarcomas. Two methylcholanthrene-induced fibrosarcomas, previously demonstrated to contain a common tumor rejection antigen(s), released infectious ecotropic murine leukemia virus and expressed the murine leukemia virus proteins, a glycoprotein with a mol wt of 70,000 (gp70) and an envelope protein with a mol wt of 15,000. To determine whether an antigen(s) specified by a murine leukemia virus might serve as a common tumor rejection antigen(s), primary cultures of syngeneic embryo cells or cultures of an allogeneic embryo cell line were infected with an endogenous ecotropic murine leukemia virus obtained from one of the cross-reacting fibrosarcomas; expression of infectious virus and/or viral proteins by infected and uninfected embryo cells was monitored and correlated with the results of transplantation protection tests. Uninfected allogeneic embryo cells (SC-1) did not release infectious virus or the viral protein gp70; mice immunized with SC-1 cells did not inhibit tumor growth. Uninfected syngeneic embryo cells did not release infectious virus but did release ug quantities of gp70 into supernatant fluids; mice immunized with uninfected syngeneic cells inhibited tumor growth in two of seven experiments. Virus-infected syngeneic and allogeneic embryo cells released both infectious ecotropic murine leukemia virus and gp70; mice immunized with virus-infected cells inhibited tumor growth in 11 of 11 experiments. Growth of the two cross-reacting fibrosarcomas was inhibited in mice immunized with virus-infected embryo cells. The results indicate that antigens coded for by endogenous murine leukemia virus may function as common tumor rejection antigens on chemically induced murine fibrosarcomas. (Author abstract) (35 Refs)

59. DETERMINANTS OF SUSCEPTIBILITY AND RESISTANCE TO FELINE LEUKEMIA VIRUS INFECTION. I. ROLE OF MACROPHAGES.

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JNCI; 67(4):889-898 1981

The role of autochthonous peritoneal feline macrophages (Mtheta) in the age-related resistance of cats to feline leukemia virus (FeLV) was investigated by a study of the functional properties and FeLV susceptibility of Mtheta from kittens and adult cats and the effect of hydrocortisone (HC) and silica on Mtheta-FeLV interactions. Although the phagocytic functions of isolated Mtheta from kittens and adults were equivalent, the mean FeLV susceptibility of Mtheta from kittens was 5x that of Mtheta from adult cats, thus establishing a direct correlation between the age-related susceptibility of cats and Mtheta from cats to FeLV. Mtheta of viremic cats were found to be infected with FeLV in vivo; virus titers were slightly higher than those obtained after in vitro infection of Mtheta. Mtheta from cats that had experienced regressive FeLV infection were not significantly more resistant to FeLV infection in vitro than were Mtheta from naive adult specific-pathogen-free cats. HC, which has been shown to enhance the in vivo FeLV susceptibility of cats, also enhanced the permissiveness of Mtheta from cats to FeLV in vitro (600-fold for Mtheta from adult cats and 200-fold for Mtheta) from kittens. Mtheta permissiveness to FeLV was highly sensitive to HC and occurred in Mtheta infected in vivo or in vitro. In parallel with the effect of HC on the natural resistance of cats to FeLV, administration of silica before virus inoculation also markedly enhanced the FeLV susceptibility of adult cats. Silica was toxic for isolated Mtheta but not for lymphocytes in vitro, and silica produced monocytopenia and neutrophilia, delayed skin allograft rejection, and augmented feline oncovirus-associated cell membrane antigen antibody responses in vivo. These experiments indicate that Mtheta were linked to the natural resistance of cats to FeLV and that the temporary elimination of Mtheta functions (eg, by silica) and/or the conversion of the Mtheta-FeLV relationship from a nonpermissive to a permissive state (eg, by corticosteroids) resulted in failure of early virus containment, in persistent virus amplification in hemolymphatic tissues, and in subsequent FeLV-related proliferative or antiproliferative disease. (Author abstract) (72 Refs)

60. DETERMINANTS OF SUSCEPTIBILITY AND RESISTANCE TO FELINE LEUKEMIA VIRUS INFECTION. II. SUSCEPTIBILITY OF FELINE LYMPHOCYTES TO PRODUCTIVE FELINE LEUKEMIA VIRUS INFECTION.

Rojko JL, Hoover EA, Finn BL, Olsen RG
Dept. Veterinary Pathobiology, Ohio State Univ., 1925 Coffey Road, Columbus, OH, 43210
JNCI; 67(4):899-910 1981

The interplay between feline leukemia virus (FeLV) and feline lymphocytes (lc) infected in vitro or in vivo was investigated. Surface marker analysis and viral infectivity (VI) assays of lc populations were used to determine susceptibility of lc subsets to FeLV. The principal FeLV-replicating cell in the mesenteric lymph node of persistently infected, preleukemic cats was a nonadherent, complement receptor (CR)-bearing lc (B-cell). The lymph nodes of preleukemic cats also had increased numbers of uninfected T-cells [cells forming rosettes with guinea pig RBC (GPE)] and cells with receptors for the Fc portion of 7S IgG (FcgammaR cells) as compared with lymph nodes of age-matched specific-pathogen-free (SPF) cats. The induction of productive infection of feline peripheral blood mononuclear WBC (PBL) in vitro depended on a 48-hr in vitro preincubation period before virus exposure. The equivalent susceptibility of whole and adherent cell-depleted PBL to productive infection and the failure of hydrocortisone to enhance viral infection were compatible with identification of the FeLV-replicating cell as an lc. Furthermore, lc from susceptible SPF kittens replicated 50x as much FeLV as did lc from resistant adult SPF cats. The lc productively infected with FeLV after in vitro exposure were more precisely identified with the use of Ficoll-Isopaque density gradient separation of rosetted and non-rosetted lc. Whole PBL, GPE rosette-positive PBL (T-cells), and CR-positive PBL (B-cells) were permissive to FeLV infection, and max VI was evident at 14 days after exposure. The substantial (1,325-fold) increment in VI found in the FcgammaR-depleted PBL suggested a role for FcgammaR cells in the containment of FeLV infection. Unstimulated mononuclear WBC from blood, spleen, lymph node, thymus, and marrow were susceptible to productive FeLV infection after in vitro exposure. The degree of spontaneous DNA synthesis in marrow, thymus, and spleen but not lymph node or PBL was inversely related to permissiveness to viral replication. Mitogen activation of lc was associated with decreased viral replication when either T-cell mitogens (concanavalin A, phytohemagglutinin, or pokeweed mitogen) or a B-cell mitogen (dextran sulfate) was used. Virus production by spleen cells and PBL was enhanced twofold to 10-fold by prior lc stimulation by the B-cell mitogen, lipopolysaccharide, or protein A-bearing Staphylococcus aureus, a mitogen for feline T-cells with FcgammaR. Both productively infected (preincubated) and nonproductively infected (freshly isolated) PBL transferred infectious FeLV to autochthonous peritoneal macrophages (Mtheta); most of the virus in PBL-peritoneal Mtheta cocultures was produced by adherent cells, irrespective of whether the adherent or nonadherent cell population was inoculated originally. (Author abstract) (49 Refs)

61. HOST AGE AND MAJOR HISTOCOMPATIBILITY GENOTYPE INFLUENCE ON ROUS SARCOMA REGRESSION IN CHICKENS.

Heinzelmann EW, Clark KK, Collins WM, Briles WE
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Poult Sci; 60(10):2171-2175 1981

The effect of host age at inoculation on Rous sarcoma virus (RSV-1)-induced tumor regression among chickens differing in major histocompatibility complex (MHC) genotype was examined. White Leghorn lines 6 subline 1 (6-1) and 15 subline 1 (15-1) and their crosses (F3 to F5) segregating for the B genotype were used. Chickens were assigned a tumor profile index according to rate of regression: TPI 1 for complete regression by 28 days, TPI 2 by 56 days, TPI 3 by 70 days or by 56 days followed by recurrence, TPI 4 with plateau and/or slight regression by 56 days, and TPI 5 for terminal tumor prior to 70 days. Tests with noninbred chickens hatched at 2-wk intervals but inoculated on the same calendar date showed that RSV inoculation at age 4 wk results in significantly less tumor regression than seen when inoculation occurs at 6, 8, 10, 12, or 14 wk. Mean TPI at 4 wk was 3.8 compared with 2.1-2.5 at all other times. When chickens were hatched at one time and groups of 30 inoculated at 2-wk intervals, mean TPI for 4 and 6 wk of age was 3.8 and 3.4, respectively, values significantly different from the mean 2.3-3.0 of all other age groups. The (6-1 x 15-1) B2/B2 chickens had a higher incidence of tumor regression than B5/B5 chickens regardless of age (overall mean TPI of 2.4 vs 4.5). Chickens of both genotypes inoculated at 6 wk had a mean TPI of 3.8 compared with 3.1 for those inoculated at 58-88 wk, a significant difference. The genetic effect of the MHC was relatively greater than that of host age at RSV-inoculation on the fate of RSV-induced tumors. (18 Refs)

62. LYMPHOCYTE SUBPOPULATIONS AND RESPONSIVENESS IN RATS BEARING INTRACRANIAL TUMORS INDUCED BY AVIAN SARCOMA VIRUS.

Roszman TL, Brooks WH, Markesbery WR, Aziz GJ, Bigner DD
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J Neurosurg; 55(4):554-559 1981

The mitogenic responsiveness of peripheral blood lymphocytes obtained from Fischer 344 rats inoculated with avian sarcoma virus was studied. In addition, quantitative alterations in lymphocyte subpopulations were determined in these animals.

Only peripheral blood lymphocytes from rats bearing astrocytomas had significantly diminished responses to concanavalin A when compared to control responses. The percentage of lymphocyte subpopulations detected in either the peripheral blood or spleen of tumor-bearing rats did not differ from values obtained with control rats. However, rats bearing astrocytomas had a marked decrease in the absolute number of the various lymphocyte subpopulations as a result of lymphopenia. Neither the sarcoma-bearing rats nor the virus-inoculated rats that did not develop tumors exhibited this lymphopenia. In addition, sera from rats bearing astrocytomas diminished the concanavalin A reactivity of spleen cells obtained from normal rats. The results of this study established the avian sarcoma virus-induced rat astrocytoma model as a useful immunological parallel for the human disease. (Author abstract) (22 Refs)

63. EVIDENCE THAT THE SPONTANEOUS BLASTOGENESIS OF LYMPHOCYTES FROM BOVINE LEUKEMIA VIRUS-INFECTED CATTLE IS VIRAL ANTIGEN SPECIFIC.

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Infect Immun; 34(1):84-89 1981

Cattle lymphocytes cultures for 3 days were found to spontaneously incorporate thymidine (3STI). Under optimal conditions of culture, the median magnitude of 3STI activity in lymphocytes from bovine leukemia virus (BLV)-infected cattle was higher than that of BLV-free cattle, but the ran ges of the values overlapped. However, the 3STI activity of most BLV-infected cattle was specifically inhibited by serum containing BLV antibodies, whereas the 3STI activity of BLV-free cattle was not. The 3STI inhibitor copurified with Ig, and its activity could be absorbed with BLV. Rabbit anti-BLV serum inhibited 3STI, but rabbit anti-BLV p25 did not. These results indicate that BLV infection induces or expands a BLV-specific lymphocyte population. Spontaneous blastogenesis may be indicative of an immune response which controls virus spread. (Author abstract) (27 Refs)

64. BOVINE LEUKEMIA VIRUS INFECTION IN A LARGE HOLSTEIN HERD: COHORT ANALYSIS OF THE PREVALENCE OF ANTIBODY-POSITIVE COWS.

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Am J Vet Res; 42(9):1474-1476 1981

Serum samples were obtained annually (from 1977 to 1980) from cows in a large Holstein herd and were tested for antibodies to bovine leukemia virus (BLV), using the agar-gel immunodiffusion test. The prevalence of reactors in the herd decreased from 23.0% to 11.8%. Analysis by 12-mo cohorts revealed that the decrease in herd prevalence was due to successive cohorts entering the herd with significantly lower BLV antibody prevalences. This was accompanied by a low annual incidence of BLV seroconversion, which ranged from 0.9% to 2.1%. (Author abstract) (22 Refs)

65. EFFECT OF COLOSTRAL ANTIBODY ON BOVINE LEUKEMIA VIRUS INFECTION OF NEONATAL CALVES.

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Am J Vet Res; 42(9):1498-1500 1981

Pairs of newborn calves were exposed to bovine leukemia virus (BLV) when they were given their 1st colostrum feeding. Calves that were given 10(6) BLV-infected lymphocytes in colostrum free of BLV-specific antibody became infected. Calves that were fed 10(7), 10(8), or 10(9) infected lymphocytes in colostrum that contained BLV-specific antibody did not become infected. One of 2 calves inoculated id with 250,000 infected lymphocytes was protected by colostral antibody, but the other was not. Colostral antibody titers in the unprotected calf decreased normally until the calf was 4 mo old and then increased markedly; this pattern indicates that the presence of colostral antibody may have prolonged the latent period of the BLV infection. (Author abstract) (18 Refs)

66. ROLE OF PROSTAGLANDIN RELEASE BY PERITONEAL MACROPHAGES AND SPLENIC ADHERENT CELLS IN IMMUNOSUPPRESSION OF AGING MICE (MEETING ABSTRACT).

Bartocci A, Maggi FM, Veronese F

National Cancer Institute, National Institutes of Health, Bethesda, MD

International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Aging related suppression of immune functions may contribute to our understanding of the pathogenesis of diseases that show peak incidence late in life like neoplasia and autoimmune disorders. Many of the earlier studies on the mechanism of loss in immunologic vigor with age were focused on macrophages (M) for its role in supressing immune response. This function seems manifested mainly by activated M through the release of several mediators including prostaglandins (PG). In this study the release of PG by peritoneal M and splenic adherent cells (SAC) from old and young BALB/c mice was compared. The levels of PGE2 and Prostacyclin (PGI2), monitored by its breakdown product 6-keto-PGF1 alpha, were measured in supernatants of 24 hr cultured adherent cells by specific radioimmunoassay techniques. We focused on PGI2 and PGE2 since in our system they represent the principal products of the arachidonate metabolism through the cyclooxygenase. Both peritoneal M and SAC from aging mice release significantly more PGE2 and 6-keto-PGF1alpha than did cells from young animals. To exploit the role of the PG release in tumor growth in aging animals, groups of 18 mo old BALB/c mice were inoculated with syngeneic fibrosarcoma cells chronically infected with Rauscher leukemia virus. The increased immunogenicity has been shown to result in the regression of the tumor in young but not in old animals. The treatment of old mice with aspirin not only increased the survival time but led in a few animals to the regression of the tumor. (no Refs)

OTHER RELATED STUDIES

67. COVERT INFECTION OF A MOUSE MAMMARY TUMOR CELL LINE WITH M. HYORHINIS: COSEDIMENTATION WITH MMTV (MEETING ABSTRACT).

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In Vitro; 17(3):207 1981

Supernatants from cultures of a mouse mammary tumor (MT) cell line were found to produce a specific cell detachment effect when inoculated into HeLa cells. The repeated attempts to cultivate this cell detachment factor (CDF) in bacteriologic, fungal, and mycoplasma media were unsuccessful. However, using the DNA fluorochrome staining technique and specific immunofluorescent staining procedures, the CDF was positively identified as a 'noncultivable' strain of Mycoplasma hyorhinis. It was also noted that this CDF could be labeled with 3H-uridine in MT cell cultures, concentrated and banded at a density of 1.18 g/cm3 when centrifuged to equilibrium in a 20-60% sucrose gradient. The salient feature of these studies is that M hyorhinis sediments at the exact density of mouse mammary tumor virus (MMTV) in sucrose gradients. This was demonstrated by sucrose gradient analyses of a purified sample of MMTV, assaying for reverse transcriptase activity, and a 3H-uridine labeled sample of M hyorhinis. The covert presence of M hyorhinis should be of particular interest and concern to researchers working with MMTV. The presence of this 'noncultivable' strain of mycoplasma in MMTV-producing cell lines could go undetected and result in the simultaneous concentration of both MMTV and M hyorhinis during routine concentration and purification procedures for MMTV. (no Refs)

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68. HIGH MOLECULAR WEIGHT GROWTH FACTOR(S) IN THE CONDITIONED MEDIUM OF 7,12-DMBA RAT MAMMARY ADENOCARCINOMA: SPECIFIC BINDING TO EGF RECEPTORS (MEETING ABSTRACT).

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Thirteenth Miami Winter Symposium: Cellular Responses to Molecular Modulators, January 12-16, 1981, Miami, Florida. University of Miami 112 pp., 1981.

Murine sarcoma virus(MSV)-transformed cells have been demonstrated to possess a reduced number of epidermal growth factor (EGF) receptors when compared to their nontransformed counterparts. This led to the discovery of sarcoma growth factor (SGF) in the conditioned medium of MSV-transformed cells. Using a similar strategy, we have found that 7,12-Dimethyl-benzanthracene (DMBA) rat mammary adenocarcinoma (RMA) cells, which are grown in primary culture in hormone defined, serum free medium, possess fewer EGF receptor sites when compared with normal rat mammary epithelial (RME) cells (25,000 versus 84,000 sites per cell, respectively). The conditioned medium (RMA-Cm) from these primary mammary cultures contains a factor(s) which competes with [125I]-EGF, but not with [125I]-insulin, for binding to its receptor on OTT-6050 mouse embryonal carcinoma cells. When the RMA-CM is filtered in 1% acetic acid, the EGF competition activity resides in 100-300 K and greater than 300K mol wt Diaflo ultrafiltration fractions. Like SGF, the RMA-CM factor(s) is acid soluble and protease sensitive. Unlike SGF, the RMA-CM factor is heat labile. In terms of its biological effects, RMA-CM is similar to SGF. The factor(s) in RMA-CM stimulates the monolayer growth of rat NRK-49F (normal rat kidney) and normal RME cells. It reduces the serum requirement of RME cells and promotes the anchorage-independent growth of NRK-49F cells in soft agar. These studies demonstrate the presence of a high mol wt factor(s) in the conditioned medium of chemically induced rat mammary adenocarcinoma cells. The factor competes specificially for EGF receptors and, like SGF, can transform normal cells - at least with respect to their ability to grow in soft agar. Both mesenchymal and epithelial cell types respond to the growth-promoting activity in RMA-CM, which may function to promote tumor cell growth as well. (1 Ref)

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RNA VIRUSES ASSOCIATED WITH CANCER

Cell Biology and Animal Studies

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VIRUS ISOLATION AND CHARACTERIZATION

1. ISOLATION OF A NEW TYPE C RETROVIRUS (HTLV) IN PRIMARY UNCULTURED CELLS OF A PATIENT WITH SEZARY T-CELL LEUKAEMIA.

Poiesz BJ, Ruscetti FW, Reitz MS, Kalyanaraman VS, Gallo RC
Lab. Tumor Biology, NCI, NIH, Bethesda, MD, 20205
Nature; 294(5838):268-271 1981

A new type C retrovirus (HTLV-mb) has been isolated from a cell line from a 64-yr-old black female patient, MB, with the leukemic phase of Sezary syndrome. This cell line, CTCL-2 was established with use of partially purified T-cell growth factor from a sample of her peripheral blood. These cells have produced typical type C particles from the earliest passage studied (passage 2) but only after induction with 5-iodo-2'-deoxyuridine. The fractions containing HTLV-mb particles were identified by electron microscopy and by assaying for reverse transcriptase. Proteins and nucleic acid of HTLV were also identified in the fresh, uncultured, Sezary leukemic blood cells from which the second isolate was obtained. Analysis of the proteins and nucleic acids of this retrovirus isolate indicate close relationship to HTLV-cr, a retrovirus recently isolated and characterized from a patient with cutaneous T-cell lymphoma (mycosis fungoides) but distinct from known animal retroviruses. (23 Refs)

2. CHARACTERIZATION BY NUCLEIC ACID HYBRIDIZATION OF HTLV, A NOVEL RETROVIRUS FROM HUMAN NEOPLASTIC T-LYMPHOCYTES.

Reitz MS, Poiesz BJ, Ruscetti FW, Gallo RC
Natl. Cancer Inst., Bethesda, MD, 20014
Haematol Blood Transfus; 26:515-516 1981

Cyclic DNA (cDNA) and 70S RNA were prepared from the novel human neoplastic T-lymphocyte retrovirus HTLV. These probes were used to determine (1) degree of relatedness to other viruses, (2) whether or not HTLV is endogenous, and (3) whether related sequences can be found in other human tissues. HTLV cDNA hybridized 90% to its own 70S RNA; it did not hybridize significantly to a variety of retroviruses including murine and feline leukemia and sarcoma viruses, baboon endogenous virus, squirrel monkey retrovirus, Mason-Pfizer virus, bovine leukemia virus, RD114 endogenous cat virus, murine mammary tumor virus, and avian myeloblastosis virus. Low (5-10%) levels of hybridization were achieved with 70S from woolly monkey virus and gibbon ape leukemia virus. No HTLV hybridization was obtained with DNA or RNA from normal human peripheral blood T-lymphocytes, with DNA from non- neoplastic autopsy tissues or peripheral blood samples from patients with acute myelogenous leukemia, chronic myelogenous leukemia, or chronic lymphocytic leukemia. DNA from 1/3 acute lymphocytic leukemias (ALL) and 1/2 Sezary syndrome peripheral blood samples hybridized a significant 20-25% of HTLV cDNA. The positive ALL was T-cell. HTLV appears to be a novel retrovirus isolate not endogenous to humans. Results suggest that it is associated with T-cell lymphomas and leukemias of mature cell type. (1 Ref)

3. GROWTH OF HUMAN NORMAL AND LEUKEMIC T CELLS: T-CELL GROWTH FACTOR (TCGF) AND THE ISOLATION OF A NEW CLASS OF RNA TUMOR VIRUSES (HTLV).

Gallo RC, De The, Lajtha L, Van Bekkum DW, McCulloch EA, Greaves MJ, Seligmann M, Brecher G, Shohet SB, Bessis M, Sachs L
Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20205
Blood Cells; 7(2):313-329 1981

Previous studies have indicated that T-cell growth factor (TCGF) is the physiological growth promoter in the immune response of T-lymphocytes, acting as the second signal (after antigen) in the immune response. A summary is presented of information on proliferation of normal T-cells in a prev iously described liquid suspension culture and proliferation of several new cell lines from patients with particular types of T-cell leukemias and lymphomas. Information on the new type-C virus designated HTLV is also summarized. Neoplastic T cells from patients with cutaneous T-cell leukemias and and lymphomas, eg Sezary syndrome and mycosis fungoides, were grown routinely with the use of purified TCGF free of phytohemagglutinin and of lymphokines other than TCGF. The neoplastic T cells responded directly to TCGF without prior in vitro activation with antigen or lectin as is necessary with normal T cells. Thus, transformed mature T cells already express TCGF receptors. HTLV were isolated from some of these new cell lines. Evidence is presented to indicate these may be the first unambiguous isolates of RNA tumor viruses from humans. These new viruses are easily distinguished from all previously isolated viruses from animals. Antibodies in sera of some patients with these diseases specifically react with proteins of these viruses. (11 Refs)

4. DNA TOPOISOMERASE ACTIVITY ASSOCIATED WITH ROUS SARCOMA VIRUS.

Weis JH, Faras AJ
Dept. Microbiology, Univ. Minnesota Medical Sch., Minneapolis, MN, 55455
Virology; 114(2):563-566 1981

A DNA topoisomerase has been discovered associated with purified virions of Rous sarcoma virus (RSV). The enzyme has been purified from Prague C strain of RSV and compared with the nuclear topoisomerase from chick embryo cells. (Author abstract) (14 Refs)

5. OCCURRENCE OF THE FELINE SARCOMA VIRUS IN PET CATS AND ISOLATION OF A NEW FESV (MEETING ABSTRACT).

Hardy WD, Zuckerman E
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

After the discovery of Feline Sarcoma Virus FeLV and the sarcoma viruses of birds and mice, it was logical to search for a feline sarcoma virus. Fibrosarcomas account for 6-12% of all cat tumors. They occur as solitary slow growing tumors in old cats and, much more rarely, as multiple rapidly growing fibrosarcomas in about 1 out of every 40 cats with fibrosarcomas. During the past 12 yr we have tested 51 cats with naturally occurring fibrosarcomas by the immunofluorescent antibody (IFA) test that we developed for the detection of FeLV. We assumed that cats with fibrosarcomas who were positive in this test had FeSV in their tumor tissue since FeSV is always accompanied by excess helper FeLV. Of the 51 cats that we tested, 38 had solitary fibrosarcomas and 23 had multicentric fibrosarcomas. All of the cats with solitary fibrosarcomas were negative in the test whereas 20 of the 23 cats with multicentric fibrosarcomas were positive. Interestingly, the 3 negative cats with multicentric fibrosarcomas and 34 of the 38 cats with s olitary fibrosarcomas were older than 5 yr of age. The median age of the FeLV-FeSV negative cats with fibrosarcomas was much greater (10 yr) than that of the FeLV-FeSV positive cats (3 yr). Thus our results indicate that FeSV induces predominantly multicentric fibrosarcomas in young cats and these cats are therefore the most likely source of new FeSV isolates. We have obtained material from 14 of the 23 pet cats with FeLV positive multicentric fibrosarcomas that we have studied. All of the 3 tumors that have been tested were FOCMA positive. Recently we have established a cell culture from the primary multicentric fibrosarcoma of an FeLV-FeSV IFA test positive cat number 3465. In addition, we have transformed cat FLF, CRFK and mink CCL64 cells, with cell free homogenates of the primary tumor and tissue culture fluids from the cultures derived from the primary tumor. The transformed cells express FOCMA on their cell membranes. Cell-free tissue culture fluid from our new isolate, HZ-FeSV, has induced a large fibrosarcoma at the site of inoculation in the one kitten inoculated. Our new FeSV isolate will be used to compare its src sequences of the 3 well characterized FeSV isolates and with the onc sequences of other avian and mammalian acute leukemia and sarcoma viruses. (no Refs)

6. BIOCHEMICAL AND IMMUNOLOGICAL STUDIES OF THE BOVINE LEUKEMIA VIRUS (BLV) (MEETING ABSTRACT).

Portetelle D, Deschamps J, Kettmann R, Bruck C, Couez D, Mammerickx M, Burny A
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Animals infected by BLV (Bovine Leukemia Virus) synthesize antibody (Ab) directed against all BLV structural proteins. Ab to BLV gp51 appear first, their titer increasing regularly until the host's death; they exhibit cytotoxic activity to BLV-producing cells. BLV gp51 was purified to homogeneity and used in radioimmunoassays run in liquid or in mixed solid-liquid phase. These techniques allowed the conclusion that many animal species, ia cattle, sheep, goat, rabbit, monkey are sensitive to BLV and can be experimentally infected. Infection of cattle, sheep and goats can lead to lymphoid tumors; infection of rabbits leads to leukopenia. We have shown that the antigenic site of BLV gp51 reacted against by the infected animal as unique and involved the carbohydrate moiety of the glycoprotein. Genetic variants of BLV were uncovered by restriction analysis of DNA of BLV-infected cells. One of these variants showed a deletion of about 5000 base pairs toward the 5' end of the viral genome. In general, the same cell clone proliferates in all tumors of a given animal. In some cases, tumors of different clonal origin were found in the same animal. The 3' ends of the provirus and flanking sequences found in two such tumors were cloned and sequenc ed. Data will be presented and discussed. (no Refs)

7. ONCOGENIC VIRUSES.

Wyke JA
Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England
J Pathol; 135(1):39-85 1981

Virus-induced cancer in animals, including man, and the molecular mechanisms of virus-induced neoplasia are reviewed. Topics discussed include the diversity of relationships between oncogenic viruses and host animals, the problem of identifying human tumor viruses, and a brief catalogue of clinically important oncogenic viruses (avian retroviruses, murine leukemia and sarcoma viruses, leukemia and sarcoma viruses of other species, mouse mammary tumor virus, retroviruses and nonneoplastic disease, papovaviruses, adenoviruses, lymphotropic herpesviruses, other herpesviruses, hepatitis B virus, and poxviruses). General features of the interactions between viruses and their host cells, the transformed cell, replication of retroviruses, and cell transformation and tumor formation by retroviruses are discussed. (85 Refs)

VIRUS ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

8. ASSOCIATION OF MICROTUBULES AND INTERMEDIATE FILAMENTS IN NORMAL FIBROBLASTS AND ITS DISRUPTION UPON TRANSFORMATION BY A TEMPERATURE-SENSITIVE MUTANT OF ROUS SARCOMA VIRUS.

Ball EH, Singer SJ
Dept. Biochemistry, Univ. Western Ontario, London, Ontario, Canada N6A 5C1
Proc Natl Acad Sci USA; 78(11,part2):6986-6990 1981

By double indirect immunofluorescence, using primary rabbit antibodies to tubulin and guinea pig antibodies to vimentin, we have simultaneously labeled microtubules and intermediate filaments in several types of cultured normal fibroblasts. With well-spread interphase cells there was an extensive but not complete correspondence of the labeling patterns for the two filamentous structures out to the cell periphery. This correspondence existed both at a gross level, where parallel but not coincident arrays of thickly labeled strands of the two types of filaments were observed, and at a fine level, where thinly labeled strands of the two were superimposed. The results suggest that there may be some type(s) of molecular linkages between microtubules and vimentin intermediate filaments that is under metabolic control. With NRK fibroblasts infected with a temperature-sensitive mutant (LA23) of Rous sarcoma virus, cells grown at the nonpermissive temperature (39 C) showed the correspondence of the distributions of the microtubules and intermediate filaments characteristic of the normal phenotype but within 1 hr after a shift to the permissive temperature (33 C) there was an extensive retraction of the intermediate filaments around the cell nucleus whereas the microtubules remained dispersed into the cell periphery. These results suggest that one of the functions carried out by p60src, the protein kinase responsible for transformation by Rous sarcoma virus, may be to modify the component(s) involved in the putative linkages between microtubules and intermediate filaments in the normal cells. (Author abstract) (26 Refs)

9. TYROSYLPROTEIN KINASE AND PHOSPHATASE ACTIVITIES IN MEMBRANE VESICLES FROM NORMAL AND ROUS SARCOMA VIRUS-TRANSFORMED RAT CELLS.

Gallis B, Bornstein P, Brautigan DL
Dept. Biochemistry, Univ. Washington, Seattle, WA, 98195
Proc Natl Acad Sci USA; 78(11,part2):6689-6693 1981

Membrane vesicles, isolated from normal and Rous sarcoma virus-transformed rat cells, have an associated cyclic-AMP independent kinase that phosphorylates a Mr 37,000 protein in vesicles from normal cells and proteins of Mr 37,000, 50,000, and 67,000 in vesicles from transformed cells. Proteins in vesicles from normal and transformed cells contain 9% and 77%, respectively, of their labeled phospho amino acids as phosphotyrosine. Thus, isolation of vesicles and subsequent incubation with [gamma-32P]ATP enriches the proportion of labeled phosphotyrosine in proteins (relative to other phospho amino acids) by two orders of magnitude over that found in intact cells. The in vitro phosphorylation of each of these proteins is enhanced in the presence of 10 uM Zn++, a phosphotyroslyprotein phosphatase inhibitor. From these studies it appears that membrane vesicles may be a valuable system for examination of transformation-specific phosphorylation of proteins. (Author abstract) (25 Refs)

10. THE SRC GENE PRODUCT (PP60SRC) OF AVIAN SARCOMA VIRUS RAPIDLY INDUCES DNA SYNTHESIS AND PROLIFERATION OF CALCIUM-DEPRIVED RAT CELLS.

Durkin JP, Boynton AL, Whitfield JF
Animal and Cell Physiology Group, Natl. Res. Council Canada, Ottawa, Ontario K1A OR6, Canada
Biochem Biophys Res Commun; 103(1):233-239 1981

Calcium-deprived tsLA23-NRK cells are reported to be blocked near the G1/S boundary of the cell cycle at 40 C, a temperature non-permissive for neoplastic transformation. Such arrested cells rapidly initiated DNA synthesis and resumed proliferating in calcium-deficient medium when the temperature was lowered to 36 C, a level permissive for the production of active pp60src and neoplastic transformation. In contrast, previous studies had shown that calcium-deprived wtB77-NRK cells grew rapidly and continuously at either 40 C or 36 C, while uninfected NRK cells were unable to proliferate at either temperature in calcium-deficient medium. The product of the src transforming gene of avian sarcoma virus may thus act near the G1/S border to rapidly bypass or directly stimulate a normally calcium-dependent process needed for the initiation of DNA synthesis. pp60src thus allows neoplastic, avian sarcoma virus-infected NRK cells to proliferate in calcium-deficient medium which does not support the proliferation of non-neoplastic counterparts. This work supports the suggestion that changes in protein kinase activities are responsible for the ability of a wide variety of transformed avian, bovine, rodent and human cells to proliferate in calcium-deficient medium. (21 Refs)

11. ABELSON VIRUS-INFECTED CELLS CAN EXHIBIT RESTRICTED IN VITRO GROWTH AND LOW ONCOGENIC POTENTIAL.

Whitlock CA, Witte ON
Dept. Microbiology, Univ. California, Los Angeles, CA, 90024
J Virol; 40(2):577-584 1981

We have designed a method for growing bone marrow cells infected with Abelson murine leukemia virus which permits examination of target cell growth early after infection. This culture system increases the efficiency of target cell growth by favoring rapid growth of a mixed population of adherent cells in the primary culture. the nonadherent Abelson virus-infected cell populations expressed pre-B-cell differentiation markers characteristic of Abelson virus-transformed cells (mu-heavy chains of Ig M and terminal deoxynucleotidyltransferase). Early after infection, these cell populations exhibited restricted in vitro and in vivo growth properties which differed from those of an established Abelson virus-transformed cell line, 2M3. These included a marked dependency upon the adherent cell layer for growth and viability, a lower efficiency of agar colony formation, and a lower capacity for tumor production in syngeneic animals. Growth of the early populations could be maintained in the absence of the adherent cell layer by using conditioned medium from long-term adherent cell cultures established in the absence of viral infection. After passage of the populations for several wk, the in vitro growth properties gradually shifted toward that of the 2M3 cell line. Twelve-wk-old populations grew independently of the adherent cell layer and showed an increased efficiency of agar colony formation. These data indicate that many lymphoid target cells exhibit an intermediate transformed phenotype when infected with Abelson virus. Growth of these cells in culture is mediated via a synergistic interaction between intracellular expression of the viral transforming gene and an exogenous growth-promoting activity which can be provided by cultures of adherent bone marrow cells. (Author abstract) (31 Refs)

12. EFFECTS OF MURINE LEUKEMIA VIRUSES ON GENERATION OF CONTINUOUS CELL LINES OF PLURIPOTENTIAL HEMATOPOIETIC STEM CELLS IN VITRO (MEETING ABSTRACT).

Greenberger JS, Sakakeeny MA, Hoffman N, Novak T
Department of Radiation Therapy, Harvard Medical School, Boston, MA, 02115
Exp Hematol; 9(Suppl9):40 1981

Transfer of nonadherent cells from corticosteroid-supplemented continuous murine bone marrow culture as early as day 7 and as late as wk 52 to conditioned medium (CM) from the WEHI-3 cell line produces permanent cell lines from AKr/J, BALB/cJ, CBA/J, C57BL/6J, C57BL/10J, C57BL/KsJ, C57BL/Ka, C57B r/cdJ, outbred Swiss CD-1, C3H/HeJ, C58/J, C57L/J, DBA/2J, SJL/J, SWR/J, or NZW cultures but not Rf/j, 129/J, NZB, outbred Swiss N:NIH(S), HRS/J, RfM/SN, or RfM/UN cultures. Replication of added ecotropic virus increased the longevity of generation of GM-CFUc in primary cultures; however, stimulation of WEHI-3 CM dependent permanent lines was only detected in cultures infected with SFFV (spleen focus-forming virus) or Abelson-MuLV containing pseudotype viruses and cell lines were only leukemogenic in vivo if SFFV or A-MuLV persisted in them. BALB/Mo long-term marrow cultures produced high titers of germ-line derived Moloney-MuLV and generated permanent cell lines at higher frequency than BALB/129 cultures infected in vitro with Moloney-MuLV. The WEHI-3 growth factor(s) purified by Amicon filtration, lyophilization, and Sephadex G100 chromatography, demonstrated a peak of activity which overlapped with WEHI-3 derived GM-CFUc CSF. In contrast, a growth factor(s) also produced by WEHI-3 cells that produced proliferation of cloned mast cell/basophil lines was separable from the GM-CFUc (CSF), and the factor for unlimited self-renewal of hemopoietic progenitor cell lines. Phenotypic properties of several virus infected and control WEHI-3 CM dependent lines revealed many to be pure granulocyte; however, some were mixed populations of toluidine-blue positive mast cell/basophil progenitor cells, granulocyte progenitors, macrophage progenitors, and erythroid colony progenitors BFUe. Macroscopic BFUe scored at days 12-14 were removed from semisolid culture and re-established permanent pluripotential lines in WEHI-3 CM. Specific murine leukemia virus infection of long-term bone marrow cultures stimulates WEHI-3 CM dependent pluripotential cell lines through effect(s) on the hemopoietic microenvironment of the primary culture. (no Refs)

13. EFFECTS OF MURINE LEUKEMIA VIRUSES ON LONG-TERM MURINE BONE MARROW CULTURES AND DERIVED WEHI-3 CONDITIONED MEDIUM-DEPENDENT HEMOPOIETIC PROGENITOR CELL LINES (MEETING ABSTRACT).

Greenberger JS
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Nonadherent (NA) cells removed from uninfected marrow cultures from each of 28 inbred strains and outbred stocks were tested for production of clones from continuous hemopoietic progenitor cell lines in WEHI-3 cell-conditioned medium (CM). NA cells removed as early as day 7 and as late as wk 52 from long-term marrow cultures of some mice (AKr/J, BALB/cJ, CBA/J, C57BL/6J, C57BL/10J, C57BL/KsJ, C57BL/KA, C57BR/CDJ, C3H/HeJ, C58/J, C57L/J, DBA/2J, SJL/J, SWR/J, NZW) but not other mouse strains (Rf/J, 129/J, NZB, and HRS/J) generated permanent lines which were cloned and produced GM-CFUc in vitro for up to 2 yr. The outbred Swiss stock cultures N:NIH(S) did not generate permanent lines while CD-1 Swiss cultures did. Following infection with: Abelson virus; Friend leukemia virus, polycythemia-inducing strain, FLVP; anemia-inding strain, FLV-A; or pseudotype viruses derived by rescue of SFFV (from FLV-P) with cloned Rauscher (R) or Moloney (M) helper viruses; but not with R or M helper viruses alone; N:NIH (S) long-term cultures generated permanent lines. The frequency of cultures generating permanent lines was increased by M infection of BALB/cJ long-term marrow cultures or with NA cells from BALB/Mo marrow cultures (having germ line integration of Moloney leukemia virus). SFFV (R-MuLV) infection of cultures from C3H/HeJ, C57BL/6J, B6, B6.S (congenic for the allele for sensitivity to polycythemia induction by FLV-P) or N:NIH (S); increased the frequency of generation of WEHI-3 cell-conditioned medium-dependent lines. (no Refs)

14. THYMIC NURSE CELLS: A SITE FOR THE INTERACTION BETWEEN RADIATION LEUKEMIA VIRUS AND THYMUS IMMATURE LYMPHOID TARGET CELLS (MEETING ABSTRACT).

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Exp Hematol; 9(Suppl9):11 1981

In the C57 BL/Ka strain of mice, the inoculation of Radiation Leukemia virus (Rad LV) results in the development of lymphomas which are selectively located in the thymus. Target cells susceptible to productive infection by Rad LV belong to a restricted subpopulation of immature lymphoid cells corresponding probably to transitional forms between T cell precursors and subpopular blast cell population. Therefore the possible relationship between Rad LV and Thymic Nurse Cells (TNC) was investigated: TNCs are those peculiar lymphoepithelial complexes recently described by Wekerle and Ketelsen which are supposed to sustain the first step of intrathymic proliferation and differentiation of the immature T cells precursors. TNC lymphoid cells were recovered from TNCs after a short in vitro incubation, treated with alpha Thy 1, alpha Ly 1, alpha Ly 2 monoclonal antibodies and a 2nd step fluorescein isothiocyanate conjugated serum and then analyzed with a fluorescence-activated cell sorter IV: their cell surface phenotype was similar to that of cortical thymocytes. Next, TNCs were analyzed during the first few days after intrathymic inoculation of Rad LV. On day 2, very scarce virus producing cells could be detected in the thymus. Using an in vitro infectious center detection assay, it was shown that only 1 in 30,000 thymocytes could produce Rad LV. Most of them were located in TNCs: indeed these complexes contained 300 x more virus producing lymphoid cells than the whole thymus cell population. Electron microscopical examination of these TNCs demonstrated that, among lymphoid cells, C type particles were budding only from the surface of blast cells. It is concluded that target cells start sustaining viral replication when they are engulfed in TNCs located in the subcapsular zone. (1 Ref)

15. MONOCYTIC AND LYMPHOID CELL TRANSFORMATION IN VITRO BY THE REGRESSING FRIEND VIRUS PSEUDOTYPE OF ABELSON MURINE LEUKEMIA VIRUS (MEETING ABSTRACT).

Hines DL

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An Abelson murine leukemia virus (A-MuLV) pseudotype was constructed by rescue of the A-MuLV genome from ANN-1 transformed non-producer cells using the helper virus (RF) of the regressing Friend virus complex. Neonatal BALB/c mice inoculated RF (MuLV) pseudotype developed leukemia in 3 to 5 wk. Skull, spine, and/or peripheral lymph node tumors were present in 60% of the animals. All animals developing leukemia within 6 wk had moderate splenomegaly and some had hepatic involvement. The tumors were composed predominatly of cells with a lymphoid morphology. The proliferating cells in primary and low passage cultures of spleen and bone marrow cells from RF (A-MuLV) leukemic mice were mixtures of lymphoid and monocytic cells. Both cell types expressed A-MuLV related antigens. The lymphoid cells were Thy-1 antigen negative and those from most animals were positive for intracellular cytoplasmic immunoglobulin detected by indirect immunofluorescence. The monocytic cells in these heterogeneous cultures were Fc receptor postive and produced lysozyme. Upon further passage in vitro or in vivo as sc tumors, the heterogeneous cell populations progressed to more homogeneous populations of either lymphoid or monocytic cells. Although the involved tissues of RF (A-MuLV) leukemic mice appear to consist predominantly of lymphoid cells, our studies indicate that RF(A-MuLV) infection leads to efficient transformation of both lymphoid and monocytic cells. (no Refs)

16. THE ROLE OF ERYTHROPOIETIN IN ERYTHROID COLONY FORMATION FROM RAUSCHER LEUKEMIA VIRUS-INFECTED MICE.

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Exp Hematol; 9(9):938-944 1981

Recent work has led to conflicting results regarding the in vitro control of erythropoiesis in mice infected with Rauscher Leukemia Virus (RLV). Some reports claimed that marrow or splenic erythropoiesis from RLV-infected mice were independent of exogenously added erythropoietin (Ep), while other reports supported the view that erythroid stem cells (CFUE) from RLV-infected mice required Ep for erythroid differentiation and proliferation. Results reported here demonstrate that CFUE cultured from RLV -inoculated mice are dependent upon Ep for erythroid differentiation. Furthermore, RLV-infected mice which had received transfusions to suppress the endogenous production of Ep not only had a reduction in spleen wt and reticulocyte percentage, but also reduced numbers of CFUE and BFUE. (Author abstract) (20 Refs)

17. PATTERNS OF CYCLIC NUCLEOTIDES AND RELATED ENZYMES IN NORMAL AND GROSS-VIRUS-TRANSFORMED RAT THYMOCYTES.

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Leuk Res; 5(4/5):413-420 1981

Cyclic nucleotide content and cyclase and phosphodiesterase activities in normal and Gross virus-transformed rat thymocytes were studied. Differences in cyclic nucleotide levels and in cyclase activities depended on how the data were expressed. Cyclic AMP (cAMP) levels were significantly lower in transformed than in normal thymocytes on the basis of protein content but no differences were apparent on the basis of cell number or DNA content. Cyclic guanosine monophosphate (cGMP) levels in transformed vs normal cells were also significantly reduced when the data were expressed per mg of protein, but significantly higher when based on cell number or DNA content. The cAMP/cGMP M ratio was 13.4 +-1.74 in transformed and 19.2 +-2.56 in normal thymocytes (p less than 0.02). Both adenylate cyclase and guanylate cyclase activities were significantly lower in transformed than in normal cells on the basis of protein content; no differences were apparent on the basis of cell number or DNA content. cAMP phosphodiesterase and cGMP phosphodiesterase activities, studied at two substrate concentrations (1 and 100 uM), were significantly higher in transformed than in normal thymocytes either per cell number, protein content, or DNA content. Normal thymocytes significantly increased cyclic nucleotide levels in response to isoproterenol, serotonin, carbamylcholine, sodium azide, and theophylline, but transformed thymocytes responded only to the latter two agents. The data indicated that cyclic nucleotide metabolism is abnormal in malignancy. (30 Refs)

18. INCIDENCE AND PHENOTYPIC HETEROGENEITY OF MOLONEY VIRUS-INDUCED LEUKEMIAS: A MULTIGENIC CONTROL.

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Blood Cells; 7(2):301-311 1981

Adults of seven inbred mouse strains were inoculated with Moloney leukemia virus (MuLV). Incidence of viremia after 2 mo ranged from 1.8% in B6 to 87% in BALB/c while incidence of leukemia after 6 mo ranged from 0% in NZB and DBA/2 to 97% in BALB/c. In individual mice, the host-virus relationship was studied further as to degree of viremia, appearance of leukemia, organ involvement, and surface phenot ype of leukemic cells. The viremia was controlled by H-2 and non-H-2 genes. Three of the H-2 genes in the I and D or T region of the major histocompatibility complex (MHC) behave like immune-response genes which control the specific antiviral immune response. Other gene(s) outside the MHC also affected virus production. Both sets influenced leukemia incidence, since leukemias occurred only in highly viremic strains. Additional non-H-2 genes not involved in viremia, were determinants in induction of malignancies, since some sensitive strains did not become leukemic despite high levels of virus. The anatomical type of MuLV-induced leukemias varied according to the non-H-2 background. As an example, most leukemias in B10 congeneic mice involved thymus and were frequently limited to this organ, whereas BALB mice preferentially developed splenic leukemias. In a given strain, leukemias arising in different individuals frequently expressed different phenotypes. It is concluded that MuLV-induced leukemia is a multistep process in which virus production is necessary, but is not sufficient in itself, to induce malignant transformation. (20 Refs)

19. MYELOPROLIFERATIVE SARCOMA VIRUS (MPSV), A NEW TOOL FOR THE STUDY OF HEMATOPOIESIS.

Le Bousse-Kerdiles MC, Jasmin C, Smadja-Joffe F, Klein B, Pragnell I, Ostertag W, Cronkite EP, Brecher G, Lajtha L, Bessis M, McCullogh EA, Bernard J, Van Bekkum DW, Moore MA, Sachs L, Varet B

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Blood Cells; 7(1):105-123 1981

Data supporting the hypothesis that myeloproliferative sarcoma virus (MPSV) is capable of transforming hemopoietic stem cells are presented: a direct involvement of the stem cell population is indicated by the large increase in stem-cell concentration in infected mice; indirect evidence from in vivo and in vitro experiments shows a partial independence of growth factors by two cell populations and may indicate that they are both derived from stem cells altered by MPSV. MPSV may be a new tool for studying the regulation of murine hemopoiesis and viral genetic information. (49 Refs)

20. POLYCYTHAEMIA- AND ANAEMIA-INDUCING STRAINS OF SPLEEN FOCUS-FORMING VIRUS DIFFER IN POST-TRANSLATIONAL PROCESSING OF ENVELOPE-RELATED GLYCOPROTEINS.

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Nature; 294(5842):663-665 1981

A virus preparation was isolated by Friend which produced a rapid erythroblastosis in certain strains of mice. Although the original virus preparation induced a slight anemia in the terminal stages of the disease, other variants, derived from various in vivo and in vitro passages of the original virus, were associated with polycythemia, and the different viruses were accordingly classified as FVA (Friend virus anemia-inducing) or FVP (Friend virus polycythemia-inducing). Another important difference between the two strains is that whereas FVP induces in infected mice cells that are capable of forming colonies in vitro in the absence of erythropoietin, colonies formed by cells derived from FVA-infected mice are erythropoietin dependent. Differences were also noted in the amount of hemoglobin present in erythroid bursts produced after in vitro infection of hematopoietic cells with FVP or FVA. Both FVA and FVP virus stocks have been shown to consist of at least two different viruses: the spleen focus-forming virus (SFFVP or SFFVA), a replication defective virus; and the Friend murine leukemia virus (F-MuLV), a replication competent virus which acts as a helper virus for replication of the defective SFFV. Here, in an attempt to correlate differences in the biological effects of the SFFVs derived from FVP and FVA stocks with biochemical properties of proteins encoded by them, we have compared the post-translational processing of the envelope glycoproteins encoded by these viruses, and have found both qualitative and quantitative differences in the processing of the envelope glycoproteins of the two virus stocks. (Author abstract) (23 Refs)

21. NORMAL AND FRIEND VIRUS SPECIFIC CELL COMPARTMENTS IN FRIEND LEUKEMIA CHARACTERIZED BY THEIR SENSITIVITY TO ACTINOMYCIN D IN VIVO.

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Blut; 43(5):287-296 1981

The sensitivity to actinomycin D (Act D) of the erythropoietin (EP)-independent erythropoiesis after polycythemia-inducing Friend virus (F-MuLV-P) infection of DBA/2 mice, especially of erythroid erythropoietic burst forming units (BFU-E), infectious centers producing cells (ICPC), and CFU-EI, a late erythroid stem cell corresponding to normal erythroid colony forming unit (CFU-E) but independent of Ep, was examined and compared to that of normal erythropoiesis. Fifteen ug/kg Act D had no effect on spleen wt and reticulocytosis, while 30 ug/kg reduced reticulocyte number and marginally affected spleen wt. Three and five doses of 60 ug/kg Act D completely suppressed reticulocytosis. In control animals, all CFU-E were Ep independent. After Act D treatment, no colony growth was seen for 3 days; then regeneration began, overshooting in the femur at day 5. All colony growth was Ep independent. Act D reduced ICPC numbers in the spleen to less than 1/10, mainly to due to the reduced spleen cellularity. Five doses of 60, 30, and 15 ug/kg Act D showed a dose-dependent reduction of CFU-E numbers in the femur and spleen. Spleen ICPC was sensitive to 5 x 60 ug/kg and possibly to 5 x 30 ug/kg. The max reduction was only about 10-fold, corresponding to reduction in organ size. The study of femur ICPC showed day-to-day variability. In comparison to normal uninfected mice, the number of stem cell (CFU-S) and culture (CFU-C) colony forming units was slightly lower in the femur of F-MuLV-P-infected mice. After Act D treatment, CFU-S and CFU-C were not significantly influenced, while the number of BFU-E increased at day 1 and 5 and was below virus-infected control at day 8. It was concluded that BFU-E were not affected in the bone marrow by Act D and showed some sensitivity in the spleen, since the rise in BFU-E concentration was not high enough to compensate for reduction in organ size. (21 Refs)

22. SMALL NUCLEAR RNAS IN CELLULAR GROWTH AND DIFFERENTIATION. I: METABOLIC ALTERATIONS SEEN IN FRIEND ERYTHROLEUKEMIA CELLS.

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J Cell Physiol; 109(2):235-241 1981

The distribution of small nuclear RNAs (snRNAs) in Friend virus-transformed murine erythroleukemia cells (FLC) was analyzed under a variety of physiological conditions with electrophoretic techniques. The presence of at least 15 snRNAs distinct from ribosomal 5.8 Svedberg (S) or 5 S were demonstrated. Nuclei from rapidly growing, quiescent, and terminal differentiated (and quiescent) cell contained the same complement of snRNAs. All snRNAs were synthesized in FLC irrespective of the physiological state of the cell; however, significant quantitative differences in the labeling pattern of snRNA were seen. Progression from rapid growth to quiescent or from a proerythroblast to a normoblast was accompanied by changes in the pattern of snRNAs in the nucleus. As cells progress from a rapid growth state to quiescence, a substantial reduction in the level of all snRNAs, except 4.5 S, occurred. The most dramatic reductions occurred in the amount of the nucleolar-specific snRNAs U3 and species 2, and in the differential reduction of the U1 species. A similar pattern was seen in differentiated cells, but with more marked decreases for U2 and 4.55 snRNAs. These results indicate that snRNA metabolism is apparently regulated in a developmentally significant fashion, both in association with changes in proliferative capacity of cells and with changes in gene expression that occur during terminal differentiation. (37 Refs)

23. EXPRESSION OF MCF VIRUSES CORRELATES WITH HELPER VIRUS-INDUCED FRIEND DISEASE (MEETING ABSTRACT).

Ruscetti S, Davis L, Feild J, Oliff A
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Helper-independent virus from a molecularly cloned stock of NB-ecotropic Friend Murine leukemia Virus (MuLV) induces in newborn mice an erythroleukemia-like disease characterized by splenom egaly and severe anemia. When various strains of mice were analyzed for susceptibility to this disease, NIH Swiss and BALB/c mice were found to be susceptible, while C57BL/6 and DBA/2 mice were resistant. F1 hybrids derived from susceptible and resistant mice were also resistant. Titers of recoverable virus in the spleen of both susceptible and resistant strains were comparable. Untreated adult NIH Swiss mice were resistant to the F-MuLV-induced disease but can be made susceptible by such pre-treatments as x-irradiation, phenylhydrazine, phlebotomy and parenteral silica. Spleen homogenates from the various mice were passaged on NIH 3T3 fibroblasts and the cells analyzed for viral protein expression by metabolic labeling and immune precipitation. An 80,000 dalton protein containing MCF-gp70-specific determinants could be detected in cells infected with spleen homogenates from all susceptible animals (NIH Swiss and BALB/c newborns as well as pretreated adults) but not from resistant mice (including untreated NIH Swiss adults), although ecotropic viral proteins were detected in all cells. An MCF virus isolated from the spleen of a newborn NIH Swiss mouse infected with F-MuLV induced erythroleukemia in 60% of infected adult NIH Swiss mice when pseudotyped with F-MuLV. When pseudotyped with amphotropic virus 4070, it induced disease in 27% of infected newborn NIH Swiss mice. Adult mice infected with F-MuLV alone or newborn mice infected with amphotropic virus 4070 alone had a very low incidence of disease. These results indicate that an erythroleukemia-like disease developing in susceptible F-MuLV-infected mice is correlated with the expression of MCF gp70-related proteins and that MCF viruses isolated from these mice are pathogenic when pseudotyped with ecotropic or amphotropic viruses. (no Refs)

24. REGRESSION AND PROGRESSION OF FRIEND VIRUS-INDUCED ERYTHROLEUKEMIA: THE ROLE OF INFECTION OF HEMATOPOIETIC PRECURSOR CELLS (MEETING ABSTRACT).

Furmanski P, Johnson CS, Marcelletti J
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

When spleen erythroid progenitor cells (CFU-E's) from Friend virus (FV) and FV-A leukemic animals were tested for productive virus infection by susceptibility to cytotoxicity with monospecific anti-virus gp70 antiserum, both were found to be infected with virus, even though FV-A spleen cells remained Epo-dependent. CFU-E's RFV-infected mice became infected within 5 days after virus-inoculation. However, by day 20 post-virus, when all the animals were leukemic, 50% of the mice had uninfected CFU-E's. The leukemias in these animals with uninfected CFU-E's subsequently regressed. The remainder of the RFV-infected mice had infected CFU-E's throughout the course of their disease, and their leukemias did not regress. In regressor RFV-leukemic mice, CFU-E's were neither erythropoietin independent, nor were they infected with virus. Nonetheless, these animals developed typical Friend leukemias, with massive splenomegaly, hepatomegaly, and large increases in the numbers of erythroid precursors in splenic tissues. To determine the mechanism for the pathology observed in Friend virus-infected mice in the absence of abnormalities in the CFU-E compartment, we carried out experiments on the interactions between macrophages and erythropoietic precursors. We found that the monolayers of normal macrophages inhibited colony formation by normal CFU-E's. In contrast, monolayers of macrophages from leukemic progessor mice stimulated colony formation by normal CFU-E's. These results suggest that infection of macrophages could, in the absence of other pathophysiological changes in the erythroid cells be responsible for enhanced erythropoiesis characteristic of the Friend virus-induced leukemias. Regression of leukemia may occur as a consequence of the elimination of the infected macrophages, effectively removing the stimulus for overproduction of erythroid cells. (no Refs)

25. FRIEND LEUKEMIA AS A MULTIPLE-STEP DISEASE.

Tambourin P, Wendling F, Moreau-Gachelin F, Cronkite EP, Lajtha L, Seligmann M, Greaves MJ, Brecher G, Gallo R, McCulloch EA
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Blood Cells; 7(1):133-144 1981

Friend virus-leukemias are shown by studies to evolve by multiple-step processes that involve different stages of malignancy. The early phase of disease is characterized by a rapid increase in erythroblastic cells with limited proliferative capacity. The second phase is associated with appearance of malignant cells with extensive proliferative capacity and autonomous growth. Friend leukemia is a valuable model for studying the progression of cells from a normal to a preneoplastic state and finally to a highly malignant state. (25 Refs)

26. POSSIBLE ROLE OF ENDOGENOUS MMTV VIRUS IN CHEMICAL MAMMARY GLAND CARCINOGENESIS IN MICE.

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Biull Eksp Biol Med; 91(9):339-342 1981

The effect of immunization with inactivated endogenous MMTV virus on the yield of dimethylbenz(a)anthracene (DMBA)-induced mammary gland tumors was studied in BALB/c mice free of exogenous virus. The animals were first administered DMBA (1 mg/day, 1.5 mo, po); then, 1 wk later, they were immunized with formaldehyde-treated suspension of MMTV. Control mice were immunized with Moloney leukemia virus (MuLV). Mammary gland neoplasms were detected in 21% of the mice immunized with MMTV, compared with 39% of MuLV-immunized mice and 40% of nonimmunized mice. The av latent period of tumor development in the MMTV-immunized mice was 119 days, compared with 88 days in the MuLV-immunized mice and 82 days in nonimmunized mice. Indirect immunofluorescence analysis showed expression of gp52 and p27 viral antigens in tumor tissues from both the immunized and the control mice. (11 Refs) (In RUS)

27. POSSIBLE ROLE OF GENETIC CELL VARIANTS IN THE VIRAL INDUCTION OF MOUSE MAMMARY TUMORS.

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In Vitro; 17(9):805-810 1981

Out of three attempts to induce neoplasia in normal C57Bl mammary epithelial cells with the mouse mammary tumor virus (MuMTV) only one presented signs of tumorigenicity. Immunofluorescence showed that virus synthesis took place in all three sublines but tumorigenicity as detected by cell aggregation viability (CAV) and transplantation into syngeneic mice failed to occur in two of them. By comparison, cells from a BALB/c spontaneous mammary tumor that do not express MuMTV were 100% tumorigenic, whereas cells from a BALB/cfC3H tumor with a 95% virus-producing cell population had a normal CAV and were tumorigenic only in 60% of the test animals. This lack of correlation suggested that many of the virus-producing cells were not neoplastic and that neoplasia might occur under virus stimulation only if a restricted population of genetic cell variants existed. Accelerated tissue culture passages of virus-free C57Bl and BALB/c normal mammary cells resulted in their spontaneous neoplasia at Passages 23 and 50, respectively; when duplicated cells cryopreserved in early passages were revived and cultivated in the same manner, neoplasia occurred at Passages 27 and 58. The similarity of the passage numbers appears to confirm the existence of genetic cell variants among the normal cell population. (Author abstract) (16 Refs)

28. DIVALENT CATION-INDEPENDENT AGGREGATION OF RAT-1 FIBROBLASTS INFECTED WITH A TEMPERATURE-SENSITIVE MUTANT OF ROUS SARCOMA VIRUS.

Wright TC, Underhill CB, Toole BP, Karnovsky MJ
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Cancer Res; 41(12):5107-5113 1981

Rat-1 fibroblasts infected with the temperature-sensitive transformation mutant LA 24 of Rous sarcoma virus have a high rate of divalent cation-independent homotypic cell aggregation when grown at the permissive temperature, 34 C. Cells grown at the nonpermissive temperature, 39 C, have a low rate of homotypic cell aggregation. Hyaluronic acid is involved in the homotypic aggregation of permissively grown cells since aggregation is blocked by either treatment of the cells with hyaluronidase or the presence of exogenously added hyaluronic acid. Despite their low rate of homotypic aggregation, nonpermissively grown cells are capable of heterotypically adhering to permissively grown cells. The formation of heterotypic aggregates is blocked by treatment of the nonpermissively grown cells with hyaluronidase but not by treatment of permissively grown cells with hyaluronidase. These results provide evidence that the divalent cation-independent aggregation of Rat-1 LA 24 cells is mediated by interactions between hyaluronic acid and other adhesive components on the cell surface. (Author abstract) (15 Refs)

29. TRANSFORMATION OF RAT THYROID EPITHELIAL CELLS BY KIRSTEN MURINE SARCOMA VIRUS.

Fusco A, Pinto A, Ambesi-Impiombato FS, Vecchio G, Tsuchida N
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Int J Cancer; 28(5):655-662 1981

Fischer rat thyroid epithelial cells (FRT) growing continuously in culture were infected with the Kirsten murine sarcoma virus KiMSV(KiMuLV) and found to produce this virus constitutively. Although the morphology of the FRT cells did not change appreciably, the cells became malignant after infection with KiMSV(KiMuLV) as shown by the growth of infected cells in semi-solid media (uninfected FRT cells did not grow) and by the tumorigenicity of infected cells when injected into syngeneic animals (uninfected FRT cells or FRT cells infected with non-transforming retro-viruses were not tumorigenic). The induced tumors morphologically resembled moderately differentiated carcinomas. Two markers of thyroid epithelial differentiation were absent in the original FRT clone and remained unexpressed after transformation. Fully differentiated rat thyroid epithelial cells (FRT-L cells) infected with another strain of the Kirsten murine sarcoma virus, the KiMSV(MolMuLV), were also transformed as demonstrated by the ability also of these cells to grow as carcinomas (after in vitro transformation) in syngeneic animals. Our results clearly demonstrate that the Kirsten murine sarcoma virus can transform in vitro cells of epithelial as well as of fibroblastic origin. (Author abstract) (29 Refs)

30. VIRAL VERSUS NON-VIRAL INDUCED YOLK SAC TUMORS IN THE RAT (MEETING ABSTRACT).

Sobis H, Van Hove L, Vandeputte M
Rega Institute, University of Leuven, Leuven, Belgium
Oncodev Biol Med; AbstractsBook,1:40 1981

Yolk sac tumors were induced in fetectomized rats by displacement of the visceral yolk sac outside the uterus with or without injection of Murine Sarcoma Virus (MSV) into the placenta. Some of the animals were immunized with MSV prior to surgery. The biological, morphological and immunological characteristics of the tumors which developed in animals injected or not with virus were compared. The results clearly indicate that MSV inoculation into the placentas of fetectomized rats plays a definite role in the induction of visceral yolk sac derived malignant tumors. This conclusion is based on the following findings: (1) the tumor incidence is significantly greater in the MSV-inoculated group; (2) the latency period is markedly shortened; (3) all the early tumors in the virus group appeared in the MSV-inoculated horn; (4) in the groups preimmunized with MSV the results were quite similar to those recorded in the rats treated with fetectomy alone; (5) only in the virus group did we observe the development of less differentiated tumors (embryonal carcinomas). The transplanted and/or in vitro cultured yolk sac carcinomas derived from primary tumors obtained in animals injected or not with MSV show the same morphology, are not immunogenic, secrete alpha-fetoprotein and express endodermal antigen. (no Refs)

31. INFLUENCE OF GENOTYPE, PROTEIN-CALORIE RESTRICITON AND THEIR INTERACTION UPON RSV-INDUCED TUMORS IN CHICKENS.

Clark KK
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Diss Abstr Int [B]; 42(3):902-B 1981

Four-wk-old chickens of 2 genotypes-B2B2 and B5B5 were either full-fed or restricted to 60% of the feed consumed by full-fed chickens of the same age. Two wk after being placed on experimental rations, chickens were inoculated with Rous sarcoma virus-1. Tumors were scored subjectively for size several times during a 10 wk period. Forty percent nutritional restriction delayed the appearance of tumor and reduced tumor size at 2 and 3 wk post-inoculation (PI). B genotype profoundly influenced tumor size. B2B2 chickens had smaller tumors between 3 and 10 wk PI than did corresponding B5B5 chickens. Nutritional restriction may retard initial growth by two possible mechanisms: (1) nutritional deprivation may inhibit antibody production, including blocking antibody, and enhance cell-mediated immunity, resulting in inhibited tumor growth, or (2) rapid tumor growth is restricted due to limited supply of nutrients to the cancer cells. Forty percent restriction did not exert an effect on immunocompetence based upon antibody production to sheep RBC and phytohemagglutinin-stimulated lymphocyte blastogenesis as measures of cell-mediated and humoral immunity, respectively. Thus a limited supply of nutrients may retard initial tumor growth. (no Refs)

32. FELINE LEUKEMIA VIRUS-INDUCED ERYTHROID APLASIA: IN VITRO HEMOPOIETIC CULTURE STUDIES.

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Exp Hematol; 9(10):990-1001 1981

Colony forming unit (CFU) assays were developed for feline granulocyte-macrophage (CFUGM), early erythroid (Day 2 CFUE), and late erythroid (Day 7 CFUE) colonies in methylcellulose medium. Feline CFUGM and both Day 2 and Day 7 CFUE were enhanced by feline macrophage conditioned medium and late CFUE often were intimately associated with macrophages. Kittens were inoculated with the Kawakami-Theilen (KT) strain of feline leukemia virus (FeLV) and sequential changes in marrow CFU determined. Erythroid aplasia, characterized by progressive non-regenerative anemia, lymphopenia, and a profound decrease in early and late CFUE but not CFUGM was induced by 3 to 5 wk after FeLV-KT inoculation. The susceptibility of kittens to FeLV-induced erythroid aplasia was strongly age-related; neonatal kittens were most sensitive and substantial natural resistance developed by 4 wk of age. The results demonstrate that FeLV-KT infection induced a rapid and selective suppression of erythroid progenitor cells and represents a suitable model of experimentally-induced acquired erythroid aplasia. (Author abstract) (54 Refs)

33. PREVALENCE AND SEQUELAE OF FELINE LEUKEMIA VIRUS INFECTION IN LABORATORY CATS.

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Div. Animal Medicine, Univ. Washington, Seattle, WA, 98195
J Am Vet Med Assoc; 179(11):1206-1207 1981

Over a 4-yr period, 1,683 pound-source cats received at a research institution were screened for feline leukemia virus (FeLV) infection, using an indirect fluorescent antibody test. Viremia was detected in 83 of the cats, for a prevalence of 4.9%. During this period, FeLV infection was detected in five kittens on a research project; lymphoma or anemia developed 6 to 17 mo after the infections were detected. It was concluded that apparently healthy cats infected with FeLV may not be appropriate for some biomedical research projects. (Author abstract) (9 Refs)

34. ROLE OF VIRUSES IN THE ETIOLOGY OF NATURALLY OCCURRING FELINE LEUKEMIA.

Essex M, Grant CK, Cotter SM, Hardy Jr WD

Dept. Microbiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115

Haematol Blood Transfus; 26:483-487 1981

The biology and natural history of the feline retroviruses and the diseases they cause are reviewed. The feline leukemia viruses (FeLV) cause several forms of leukemia and lymphoma that occur at different rates in different geographic areas; no specific association between naturally occurring disease and any strain(s) of any subgroup(s) has been demonstrated. FeLVs are replication competent and cause no visible pathology in infected cultured cells. FeLVs are transmitted in a contagious manner. Approx 2-5% of infected cats become persistently viremic, and one-fourth to one-third of these animals develop leukemia (the other develop infectious peritonitis, septicemia, or glomerulonephritis). Both leukemic and persistently viremic cats release large amounts of infectious FeLV in their saliva. FeLV appears to play an important role in the etiology of 'virus-negative' leukemia in cats; an understanding of the mechanism of this phenomenon may help us to explain human leukemias that occur in individuals that do not harbor replicating virus. FeLV particles contain seven distinct proteins, several of which have greater than 1 antigenic determinant and all of which induce immune responses in cats to some degree. The feline oncornavirus-associated cell membrane antigen (FOCMA) is found on lymphoma and/or leukemia cells, and the immune response to it is correlated with protection against development of leukemia and lymphoma. Two general classes of tumor- and transformation-specific antigens have been found. (39 Refs)

VIRUS REPLICATION AND EXPRESSION

35. MORPHOLOGICAL AND MICROBIOLOGICAL SIGNS OF ENDOGENOUS C-VIRUS IN HUMAN OOCYTES.

Larsson E, Nilsson BO, Sundstrom P, Widehn S

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Int J Cancer; 28(5):551-557 1981

Human oocytes in different stages of maturation were obtained by follicular aspiration from women given Clomovid and Gonadex. Particles similar to type-C virus were observed in 3 out of 16 oocytes. The particles were irregularly distributed along the oocyte membrane. They were seen both in a state of budding and lying free in the perivitelline space. Reverse transcriptase activity was detected in three out of nine samples of follicular fluid obtained from women other than those donating the oocytes. The supernatants from bat lung cells and dog thymus cells cultivated with oocytes or follicular fluids were tested for reverse transcriptase. An increased activity was observed only transiently in one case. It is assumed that these findings indicate the expression of endogenous retroviruses in human oocytes. (Author abstract) (20 Refs)

36. XENOTROPIC TYPE C VIRUS EXPRESSION IN MURINE THYMOMAS INDUCED BY RADIATION OR 3-METHYLCHOLANTHRENE.

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Virology; 114(2):580-584 1981

Thymic lymphoma incidence and thymic expression of MuLV with xenotropic infectivity was monitored in AKR, RF and reciprocal F1 mice of the AKR x RF cross after treatment with either gamma radiation or the chemical carcinogen 3-methylcholanthrene (MCA). These two inbred strains and the F1 hybrids developed similarly high incidences of thymoma, and lymphomatous cells from AKR mice and (AKR male x RF female)F1 mice were observed to be expressing MuLV with xenotropic host range. However, lymphoma cells from RF mice and (RF male x AKR female)F1 mice did not shed xenotropic MuLV. Thymic xenotropic virus expression was therefore not correlated with a high incidence of radiation or chemically induced thymoma, but rather appeared to be a phenotype genetically transmitted by AKR mice to F1 mice of the AKR x RF cross as a dominant trait in induced thymomas. In addition, a maternal effect on thymic xenotropic virus expression in induced thymomas was observed by the comparison of reciprocal F1 hybrids in this cross. (Author abstract) (7 Refs)

37. INDUCTION OF LYMPHOMA IN ANTIGENICALLY STIMULATED ATHYMIC MICE.

Baird SM, Beattie GM, Lannom RA, Lipsick JS, Jensen FC, Kaplan NO

Dept. Pathology, Veterans Admin. Medical Center, San Diego, CA, 92161

Cancer Res; 42(1):198-206 1982

Athymic mice infected with pinworms or carrying human tumor xenografts frequently develop a lymphoproliferative disorder which eventually leads to lymphoma. By immunofluorescent analysis of involved tissues, the lymphomas appear to be mixtures of null cells, B-cells, and T-cells. When each lymphoma is established in tissue culture, a predominant cell type grows out. We have now established lymphoma lines of null cells, B-cells, and T-cells. Lymphoma development is preceded by the secretion into the bloodstream of large amounts of murine leukemia virus mol wt 70,000 glycoprotein antigen; however, very little virus is produced. In vivo, the expression of viral envelope antigen appears within a few days after human tumor transplantation and precedes the development of lymphoma by about a mo. Cells expressing viral antigens are first seen in the diffuse cortex of lymph nodes and the periarteriolar white sheath of the spleen, the tissue domains in which lymphomas also first appear. (Author abstract) (21 Refs)

38. STUDIES ON THE RESISTANCE OF THE C57BL/6 MOUSE STRAIN TO THE POLYCYTHEMIA-INDUCING STRAIN OF THE FRIEND VIRUS (FV-P).

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Blut; 42(3):173-182 1981

The effect of Friend virus (FV-P) infection on normally resistant C57Bl/6 mouse cells was studied under various conditions. DBA/2 mice exposed to lethal (800 R) irradiation followed by transplantation of C57Bl/6 bone marrow cells showed an increase of erythroid progenitor (BFU-E) cells in S-phase to 75% compared with 27% in controls. No significant differences were noted in BFU-E in S-phase cells between normal DBA/2 (24.3%) and C57Bl/6 mice (25.1%). C57Bl/6 BFU-E cells transplanted into lethally irradiated DBA/2 mice were partially susceptible to FV-P infection, producing erythropoietin (EP)-independent colony growth in bone marrow and spleen of only 37% when transplanted 3 days after infection. When infection occurred after transplantation, no EP-dependency, splenomegaly, or reticulocytosis was found. C57Bl/6 cells transplanted into lethally irradiated C57Bl/6 mice also showed increased susceptibility to FV-P infection, as indicated by EP-independent BFU-E growth. Stimulation of BFU-E in C57Bl/6 mice was attempted with 150 R, bleeding, 25 ug endotoxin, or 2 x 500 mg hydroxyurea/kg. Loss of resistance and development of leukemia occurred only after treatment with endotoxin, which did not affect BFU-E levels. Results indicate that factors in addition to BFU-E levels are involved in resistance or susceptibility of mouse strains to FV-P infection. (28 Refs)

39. EXPRESSION OF THE MURINE MAMMARY TUMOR VIRUS IN THE MILK OF F1 HYBRIDS OF VIRUS NEGATIVE MOUSE STRAINS.

Bentvelzen P
Radiobiological Inst. TNO, Rijswijk, The Netherlands
Eur J Cancer Clin Oncol; 17(8):883-888 1981

Milk samples of multiparous females from several mouse strains and their F1 hybrids were tested for the presence of the envelope glycoprotein gp52 of the murine mammary tumor virus. F1 hybrids resulting from matings of the virus negative strain BALB/c with the virus negative strains AKR, ND2 or RFM were positive for the viral antigen. The progeny of backcrosses to either parent had considerable lower incidences of viral antigen-positive milks. It was concluded that different recessive genes in the BALB/c strain on the one hand and in the AKR, ND2 and RFM strain on the other cause inhibition of endogenous virus expression. In F1 hybrids the two sets of genes complement each other, resulting in virus release. (Author abstract) (31 Refs)

40. DECAY OF MOLONEY LEUKEMIA VIRUS PRODUCTION AFTER ENUCLEATION OF CHRONICALLY INFECTED MOUSE CELLS.

Ber R, Fenyo EM, Nexo BA, Skoog L
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Isr J Med Sci; 17(8):690-696 1981

The effect of enucleation of synthesis of Moloney leukemia virus was studied in chronically infected YACIR-A9 mouse hybrid cells. The synthesis of infectious virus decreased gradually until, 12 hr after enucleation, virtually no infectious virus was produced. As determined by particle-bound p30 and reverse transcriptase, cytoplasts produced a low level of noninfectious viral particles. Thus, the assembly of virus particles does not appear to be wholly dependent on the presence of the cell nucleus. In contrast, production of infectious particles shows an absolute requirement for the cell nucleus. (Author abstract) (29 Refs)

41. IN VITRO STUDIES OF A CO-CARCINOGENIC EFFECT OF VACCINIA AND HERPES GROUP VIRUSES.

Mazurenko NP, Merekalova ZI, Pavlish OA, Bykovsky AF, Kurzman MJ, Mazurenko NN
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Neoplasma; 28(4):403-412 1981

The results of studies of a co-carcinogenic effect of two human infectious viruses in tissue culture are reported here. Viable vaccinia virus actively replicating in the cells of primary BALB/c tissue culture and in a number of continuous murine cell lines has been shown to induce in them expression of major structural p30 proteins of murine retroviruses. Vaccinia virus has been also shown to cause biochemical transformation of murine cells. Evidence for the capacity of herpes simplex virus Type 2 to induce malignant transformation of BALB/3T3 murine cell line has been obtained and confirmed by transplantation to mice. Transformed cell clones did not contain complete infectious herpes simplex virus but were resistant to superinfection with this virus. N-tropic endogenous murine retrovirus of C type with buoyant density in the saccharose density gradient of 1.18 g/cm3 and a reverse transcriptase activity was expressed in the transformed cells. In the virion structure six proteins typical of these viruses with the prevalence of p30 have been demonstrated. Competitive radioimmunoassay revealed a very high level of virus production: p30 level reached 7,500 ng p30 R-MuLV per mg of viral protein. Specificity of this result was shown in control experiments. (Author abstract) (30 Refs)

GENETICS

42. ISOLATION OF TWO VARIANTS OF DUAL ECOTROPIC AND XENOTROPIC RETROVIRUS FROM THYMUSES OF MICE INOCULATED AS NEWBORNS WITH GROSS PASSAGE A LEUKEMIA VIRUS (MEETING ABSTRACT).

Youn JK, Hayat MS
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Two variants of dual ecotropic and xenotropic Retrovirus were isolated from thymuses of C3HeB/Fe mice inoculated as newborns with Gross Passage A leukemia virus (GPAV). The first variant, Th2P1, was isolated from a mouse having definite leukemic symptoms and the second, Th4P1, was from a mouse in preleukemic phase without leukemic symptoms. Both viruses replicated as efficiently in mink cells as in mouse cells, for which they showed the same N tropism as GPAV. They did not trigger formation of syncytium in XC tests. Th2P1 virus induced foci of cytopathic effect in mink cells. Th4P1 virus possessed helper activities vis-a-vis both S+L- mink and S+L- mouse cells and was neutralized significantly not only by anti-xenotropic virus serum but also by anti-ecotropic virus serum. Both viruses were devoid of leukemogenic activity when inoculated into susceptible newborn mice. However, they accelerated significantly appearance of leukemia in GPAV infected C3HeB/Fe mice as well as in AKR mice. Recombinants between exogenous ecotropic GPAVs and activated endogenous xenotropic viruses were postulated. (no Refs)

43. REPLICATION-COMPETENT F-MULV OF ANEMIC STRAIN OF FRIEND LEUKEMIA VIRUS COMPLEX CONVEYS ITS RESCUED MURINE SARCOMA VIRUS GENOME TO PROERYTHROBLASTS TO PRODUCE SPLEEN FOCI (MEETING ABSTRACT).

Ikawa Y, Sagata N, Matsugi T, Aida M, Soma GI
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Replication-competent Friend murine leukemia virus (F-MuLV) DNA was cloned in a plsmid by a recombinant DNA technique from an original anemic strain of Friend leukemia virus (FLV) complex, and thus a molecularly cloned F-MuLV, designated as 57 virus, was recovered from the NIH/3T3 cells transfected with this plasmid-cloned F-MuLV. When injected immediately after birth, this 57 virus could induce erythroblastosis with a long latency even in C57BL/6 mice with high FV-2 restriction. F-MuLV-stimulated erythroblastoid cells in the spleen were free from gp55 encoded by replication-defective spleen focus-forming virus (SFFV) of either anemic or polycythemic strain of FLV complex, and were incapable of growing in the soft agar medium. These cells were not taken to the syngeneic hosts. When the 57 virus-rescued Moloney murine sarcoma virus (MSV) was injected to adult DDD mice, it caused classical spleen foci of Friend erythroleukemia like FLV complex or myeloproliferative virus, a variant of M-MSV, and the cells of these spleen foci could grow in the soft agar medium. Establishment of cultured lines from these cells are currently being attempted. In contrast, M-MuLV-rescued MSV genome could not induce erythroblastosis when injected ip, although in our previous observation M-MSV could induce erythroblastosis when injected iv into ICR/Swiss mice. The 57 virus-rescued SFFV from a polycythemic strain of FLV selected in long passage through DDD mouse strain could induce Friend erythroleukemia with slight anemia. The M-MuLV-rescued SFFV was less efficient in induction of Friend erythroleukemia. In conclusion, the molecularly cloned F-MuLV (57 virus), being capable of inducing reactive proliferative of immature erythroblasts by its persistent infection when injected into newborn mice, can convey its rescued M-MSV genome more selectively to proerythroblastosis cells of adult mice to induce neoplastic proliferation of the cells. (1 Ref)

44. GENETIC RESTRICTION (FV-1 AND FV-2) OF IN VITRO ERYTHROID TRANSFORMATION BY FRIEND POLYCYTHEMIA VIRUS (FVP). (MEETING ABSTRACT).

Hankins WD, Luna J
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

An in vitro transformation system which may be useful in elucidating the mechanism by which FVP causes erythroleukemia in mice has recently been described. Using this in vitro system, we have examined two genetic loci, Fv-1 and Fv-2, which are responsible for resistance to the in vivo effects of FVP in certain strains of mice. Different genetic stocks containing identical spleen Focusing Forming Viruses (SFFV) were prepared by superinfecting an SFFV nonproducer clone with either B-tropic or NB-tropic helper Murine leukemia Viruses (MuLV). The B- and NB-tropic pseudotypes produced by the superinfected cells were tested for their ability to transform marrow cells from Balb/c (Fv-1b, Fv-2s), DBA2 (Fv-1n, Fv-2s), Balb x D BA F1 hybrids, and C57/B1 (Fv-1b, Fv-2r). N- and NB-tropic infectious plasma preparations were also tested. N- and B-tropic viruses induced the development of erythroid bursts only in N-type (DBA/2) and B-type (Balb/c) marrow, respectively. Neither virus preparation was active in the Balb x DBA F1 hybrid marrow. On the other hand, the NB-tropic stocks were active on marrow from DBA/2, Balb/c, and the hybrids. None of 4 virus preparations induced erythroid burst formation in C57/B1 marrow. Mixing experiments (resistant and susceptible marrows) indicated the Fv-2 restriction was intracellular rather than intercellular. Control studies with the hormone, erythropoietin, demonstrated that the C57/B1 marrow was erythropoietically active in vitro. These results demonstrate that FVP-induce erythroid burst transfomation is under genetic control at the Fv-1 and Fv-2 loci and provide a system for an in vitro analysis of the genetic restrictions. (1 Ref)

IMMUNOLOGICAL STUDIES

45. USE OF HYBRIDOMA-RESISTANT VARIANT CELL LINES TO STUDY H-2DB/FMR-SPECIFIC CYTOTOXIC T CELLS.

Chapdelaine JM, Rajan TV, Nathenson SG, Lilly F
Dept. Genetics, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Immunogenetics; 14(5):429-436 1981

An H-2Db heterozygous tumor cell line and a variant subclone bearing a mutant gene product were used to analyze the H-2Db specificity of cytotoxic T lymphocytes (CTL) generated during a Moloney murine sarcoma virus (MSV) infection. When the mutant cells were used as targets for MSV-specific CTL, the amount of cell lysis, compared with that seen with the nonmutant parental cells, was drastically decreased. However, cells of the mutant clones remained susceptible to allogeneic CTL specific for the nonmutant H-2Db molecule. The mutant cells also did not differ from the parent cells in their level of viral antigen expression. Biochemically the parental and mutant molecules were similar but not identical. The data indicate that minor alterations of the H-2 antigens caused by somatic mutation may prevent virus-infected cells from being recognized as targets by CTL. (Author abstract) (18 Refs)

46. T CELL TOLERANCE AND TUMOR PROGRESSION INDUCED BY THE NEONATAL INJECTION OF MOLONEY MURINE LEUKEMIA VIRUS (MEETING ABSTRACT).

Collavo D, Zanovello P, Ronchese F, Biasi G
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Tumors induced by Moloney Murine Sarcoma Virus (M-MSV) evolve rapidly at the site of inoculation but undergo spontaneous regression in immunocompetent hosts. This phenomenon has been shown to depend mostly on T lymphocyte reactivity. However, in mice injected neonatally with Moloney Murine Leukemia Virus (M-MuLV-carrier mice) we have found that the resulting tumors did not regress and cytolytic T lymphocytes (CTL) were not generated in vitro. Since M-MuLV and M-MSV possess common antigens, these findings suggest that the T lymphocytes were tolerized following the introduction of the virus at an early stage of development. In fact, we observed that both T and B lymphocytes from carrier mice expressed M-MuLV-induced cell surface antigens as early as a few days after neonatal virus injection. The unresponsiveness observed in these mice cannot be ascribed to the presence of suppressor cells since cell mixing experiments indicated that spleen cells from progressor mice did not inhibit the generation of M-MSV immune cytolytic T lymphocytes either in vivo or in vitro. In addition, by using a limiting-dilution system to obtain CTL clones specific for M-MuLV cell surface antigens, we observed that the frequency of CTL clones in M-MuLV carrier mice was very low compared to the frequency determined for normal mice. Finally, following intrathymic injection of M-MuLV in adult mice, we observed that a subpopulation of T lymphocytes in the spleen and lymph nodes expressed virus-induced cell surface antigens, and that autoreactive, virus-specific CTL were generated. (no Refs)

47. RELEVANCE OF ENDOGENOUS TYPE C RETROVIRUS ON M-MSV ONCOGENESIS: EXPRESSION OF ENDOGENOUS M-MULV AND NATURAL ANTIBODY PRODUCTION ASSOCIATED WITH RESISTANCE TO TUMOR INDUCTION (MEETING ABSTRACT).

Chieco-Bianchi L, E'Andrea E, De Rossi A, Salmi R
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Previous work has shown that mice which express high titers of endogenous type C ecotropic retrovirus are partially or totally resistant to tumor induction by Moloney murine sarcoma virus (M-MSV). To further investigate the role of endogenous virus in M-MSV oncogenesis, BALB/Mo mice, which carry the Moloney murine leukemia virus (M-MuLV) as an endogenous, genetically transmitted virus on BALB/c background, were studied. Groups of BALB/Mo and conventional BALB/c mice were injected im with M-MSV at different ages (3-6 wk). As expected BALB/c mice were fully susceptible to M-MSV tumor induction, and all developed tumors in one wk. On the contrary, in 6 wk old BALB/Mo mice tumors appeared only in 17% of mice and after a prolonged latent period. A certain degree of resistance was also present in 3 wk old BALB/Mo mice as revealed by a longer tumor latency than in age-matched BALB/c mice. To elucidate the possible mechanisms underlying the resistance, BALB/Mo mice were tested for M-MuLV expression at different ages by the UV-XC plaque test. It was found that tumor resistance paralleled the time course of M-MuLV activation since mice became virus positive starting at 2 wk of age and all mice were positive at 8 wk. Furthermore, normal BALB/Mo sera tested for antibody production against M-MuLV surface determinants, using a 125I-protein A binding assay, disclosed a relevant degree of binding capacity already present in some 3-4 wk old individuals and which increased further with age. An additional study carried out in female BALB/J x male (BALB/J x BALB/Mo) Bcl hybrids also showed a closely correlated pattern between M-MuLV expression, antibody production and M-MSV tumor resistance. (1 Ref)

48. TREATMENT OF FELINE LYMPHOSARCOMA AND FELINE LEUKEMIA VIRUS (FELV) BY EX VIVO IMMUNOSORPTION USING STAPH. AUREUS COWAN I: EFFECTS ON CIRCULATING IMMUNE COMPLEXES, COMPLEMENT, AND TUMOR ANTIBODY (MEETING ABSTRACT).

Jones FR, Yoshida LH, Hardy WD, Good RA, Day NK
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

FeLV is the etiologic agent of cat lymphosarcoma (LSA). Spontaneously occurring FeLV-IFA positive, LSA or FeLV-IFA positive, tumor-free pet cats were treated by low-dose, whole-body irradiation and ex vivo immunosorption using Staphylococcus aureus Cowan. Cats responded by reduction of tumor and in several cases, a complete and long-lasting (one yr or more) regression. Most importantly, there were cases of FeLV-IFA positive cats that changed to a FeLV-IFA negative status. In vitro studies of the cat's sera indicate a decrease of circulating immune complexes detected by Raji cell radioimmunoassay from pre-treatment to post-treatment (eg 1128 to 288; 792 to 24; 2320 to 200; 368 to 240 ug equivalent cat aggregated gammaglobulin/ml respectively; normal value 85 +/-65 ug/ml). There was a commensurate increase in the level of total hemolytic complement (18 to 50; 17 to 25; 8 to 60; 59 to 90 CH50 units/ml respectively; normal value 92 +/-27). There was an increase in antibody to the cat LSA tumor-specific antigen Feline Oncornavirus cell membrane antigen (FOCMA) from undetectable prior to treatment to titers less than or equal to 1:4 after treatment which corresponded to LSA regression and reversal of FeLV infection. These data suggest an immune response of the host as part of the mechanism for tumor regression and anti-viral response. The effects of irradiation alone and immunosorption alone are presently being investigated. (1 Ref)

49. IMMUNOPREVENTION OF TYPE-C VIRUS-INDUCED MURINE LEUKEMIAS BY VACCINATION WITH VIRAL ENVELOPE POLYPEPTIDES (MEETING ABSTRACT).

Hunsmann G, Schneider J
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Prevention of virus-induced murine leukemia was attempted by active immunization with subunit vaccines in two different models: erythroleukemia developing in STU mice after experimental injection of Friend virus complex and spontaneous thymic leukemia of AKR mice. Highly purified envelope polypeptides prepared from Friend (FLV)-, AKR- and feline (FeLV) leukemia virus were emulsified in incomplete Freund's adjuvant and used as immunogens. First results showed that 20/20 STU mice immunized with 100 ug of FLV gp85 survived a challenge dose of FLV inducing fatal erythroleukemia in 90-100% of unvaccinated controls, while 3/7 animals receiving 10 ug of FLV gp85 died with leukemia. Smaller doses were either ineffective, as was adjuvant alone, or even shortened the survival time. Immunization with 100 ug of FLV gp71 was inferior to the same dose of gp85, (2/6 mice died after challenge) but was superior to isolated p15E. Only the immune response to glycoprotein 71 seems to reduce mortality and is probably developed more strongly when gp85 is used as immunogen. The internal core protein p30 and adjuvant alone were ineffective as vaccines. (no Refs)

50. FRIEND LEUKEMIA VIRUS INDUCED IMMUNOSUPPRESSION: REVERSAL BY BACTERIAL PRODUCTS AND ACTIVATED MACROPHAGES (MEETING ABSTRACT).

Friedman H, Specter S, Butler C, Bendinelli M
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Recent studies in this laboratory have shown that components of the Friend leukemia (FL) complex have varying effects on different cell types in infected animals. In vitro studies have focused attention on the likelihood that suppression of B cells involved in antibody responses may be mediated, at least partially, by the interaction of the virus with macrophages which serve as accessory cells and the source of immunoregulatory monokines. In this regard, normal lymphoid cells from non-infected animals, when added in co-culture experiments to lymphoid cells from FLC infected mice, reversed both the immunosuppressive and leukemogenic activities of the infected cells. Macrophages, as well as adherent lymphoid splenic cells when activated in vitro with a variety of bacterial components such as endotoxins or lipoteichoic acid, as well as BCG, Corynebacterium parvum, muramyl dipeptides, etc, acquired the ability to reverse the immunosuppression and leukemogensis associated with FLC infection. Furthermore, cell free culture supernatants from stimulated macrophages in vitro had the ability to enhance the antibody responses of FL infected spleen cell cultures in vitro. Culture supernatants, rich in monokines, were most active in reversing immunosuppression and leukemogenesis. Furthermore, purified lymphokines derived from a continuous cell line of lymphoid cells, when either injected into virus infected animals or added to cultures of virus suppressed lymphoid cells, partially reversed the immunosuppression associated with FL virus as well as depressed the leukemogenic potential of the virus. Therefore, it appears likely that whereas FLC and its components have the ability to interact with specific cells of the immune system, markedly altering normal immune function, various other cell populations as well as soluable factors derived from such cells can, in turn, reverse some or all of the immunosuppressive and leukemogenic properties of the virus. (no Refs)

51. RECOVERY FROM FRIEND VIRUS LEUKEMIA IS INFLUENCED BY RFV-1 (H-2D) GENE CONTROL OF THE KINETICS OF THE VIRUS-SPECIFIC T LYMPHOCYTE RESPONSE (MEETING ABSTRACT).

Britt WJ, Chesebro B
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Because mice of both Rfv-1 genotypes are capable of generating anti-Friend Virus (FV) cytotoxic T lymphocytes (CTL) following recovery, the Rfv-1 gene does not appear to control the absolute ability to generate FV-specific CTL. However, this gene might operate by influencing the magnitude or kinetics of the T lymphocyte response. In order to examine this question we developed a lymphocyte proliferative assay which detected FV-specific T lymphocytes in both leukemic and recovered mice. T lymphocyte enriched spleen cells were obtained by passage of spleen cells over nylon wool columns. The T lymphocyte enriched spleen cells were then mixed with mitomycin C treated FV leukemia cells, incubated for 4 days and the uptake of 3H-thymidine was determined. When the kinetics of the T lymphocyte proliferative response to FV leukemia cells was studied, the majority of Rfv-1b/b mice developed a significant response as early as day 6 after virus inoculation, and by day 10 post-virus inoculation greater than 90% (14/15) of Rfv-1b/b had a significant T lymphocyte response. In marked contrast, only a small minority (10%) of Rfv-1b/d mice exhibited a significant T lymphocyte respone to FV leukemia cells by day 14 after FV inoculation. However, greater than 80% (15/17) of Rfv-1b/d mice had developed a significant T lymphocyte response by day 16 after virus inoculation in spite of the continued presence of leukemic splenomegaly. The T lymphocyte response in Rfv-1b/d was comparable in magnitude to Rfv-1b/b mice. Thus, Rfv-1b/b mice developed a significant T lymphocyte response to FV about 6-8 days earlier than Rfv-1b/d mice. (B10.A(1R) X A.BY)F1 mice with a recombination to the left of the H-2D region also developed a significant T lymphocyte response on day 10 after FV inoculation. These results suggested that the H-2D (Rfv-1) gene not only controlled the ability to recover from FV leukemia but also influenced the kinetics of the FV-specific T lymphocyte response following FV in oculation. Thus, the kinetics of this T lymphocyte response appeared to be quite important for recovery from FV leukemia. However, the presence of this response did not insure recovery from FV leukemia when it occurred later than 16 days post-FV inoculation as in Rfv-1b/d mice. (no Refs)

52. RELATIONSHIP OF THE FELINE ONCORNAVIRUS ASSOCIATED CELL MEMBRANE ANTIGEN TO A FELINE SARCOMA VIRUS ENCODED POLYPROTEIN.

Snyder HW, Dutta-Choudhury M, Hardy Jr WD
No affiliation given
Haematol Blood Transfus; 26:488-491 1981

Using immunoaffinity chromatography on a column of Sepharose containing bound IgG from cat anti-feline oncornavirus-associated cell membrane antigen (FOCMA) serum, a 70,000-dalton protein was isolated from lysates of mink cells transformed by the Gardner-Arnstein strain of feline sarcoma virus (GA-FeSV). This result was unanticipated because previous evidence had suggested that FOCMA was associated with the much larger (95,000 dalton) gag-x fusion protein in these cells. The GA-FeSV gag-x protein was also isolated by virtue of its binding to anti-FeSV antibodies on a different affinity column. Preliminary biochemical characterization of the 70,000-dalton protein from both GA-FeSV-transformed mink fibroblasts and feline lymphosarcoma cells showed no differences between them. The gag-x protein was distinguishable by labelling with 32P-orthophosphate, association with protein kinase activity, and its precipitation ability with antibodies in a hyperimmune antiserum to FeLV structural proteins. It is hypothesized that FOCMA may actually be a family of antigens, not all of which cross-react with FeSV polyprotein antigens. (21 Refs)

53. ROLE OF COLOSTRUM AND MILK IN THE NATURAL TRANSMISSION OF THE BOVINE LEUKEMIA VIRUS.

Ferrer JF, Piper CE
Comparative Leukemia Studies Unit, New Bolton Center, Sch. Veterinary Medicine, Univ. Pennsylvania, Kennett Square, PA, 19348
Cancer Res; 41(12):4906-4909 1981

The role of colostrum and milk in the transmission of the bovine leukemia virus (BLV) was examined by monitoring the development of BLV infection in calves that were fed since birth on colostrum and milk from their BLV-positive dams and then reared in complete or partial isolation from infected cattle. Twenty-one of the 25 calves raised in complete isolation remained negative for BLV until the last evaluation. At this time, 14 calves were older than 28 mo of age, and 7 were 16 to 20 mo old. Three calves in this group became BLV positive before the age of a 5 mo, and one became so at the age of 12 mo. Of the 16 calves raised in partial isolation, 2 were positive at the ages of 11 and 18 mo, respectively. The other 14 calves remained negative during the 26 to 29 mo of observation. It is not known if the six animals that became BLV positive in these two groups were infected by milk, or prenatally, or during contact with their infected dams. While only 6 of the 41 calves raised in isolation became infected, all 18 calves raised in contract with BLV-positive cows became infected before the age of 26 to 29 mo of age, and 12 were positive at 16 to 20 mo of age. Thus, it is apparent that, under natural conditions, milk-borne transmission of BLV, if it occurs at all, is much less frequent than contact transmission, despite the fact that, as shown in previous studies, infectious BLV is present in the colostrum and milk of most BLV-positive cows. Passively acquired maternal antibodies to BLV were probably responsible for the resistance of the calves to milk-borne infection. (Author abstract) (21 Refs)

OTHER RELATED STUDIES

54. COVERT INFECTION OF A MOUSE MAMMARY TUMOR CELL LINE WITH MYCOPLASMA HYORHINIS: COSEDIMENTATION WITH MOUSE MAMMARY TUMOR VIRUS IN SUCROSE DENSITY GRADIENTS.

Sydiskis RJ, Weber PA, Del Giudice RA
Dept. Microbiology, Univ. Maryland Dental Sch., Baltimore, MD, 21201
In Vitro; 17(11):997-1003 1981

Supernatant fluids from cultures of a mouse mammary tumor (MT) cell line were found to produce a specific cell detachment effect when inoculated into HeLa cells. The cell detachment factor (CDF) responsible for this effect was examined. Repeated attempts to cultivate this CDF in bacteriologic, fungal, and mycoplasma media were unsuccessful. However, using the DNA fluorochrome staining technique and specific immunofluorescent staining procedures, the CDF was identified positively as a noncultivable strain of Mycoplasma hyorhinis. It was also noted that this CDF could be labeled with [3H]uridine in MT cell cultures, concentrated, and banded at a density of 1.18 g/cm3 when centrifuged to equilibrium in a 20 to 60% sucrose gradient. Using a multiple antibiotic treatment regimen, the MT cells were 'cured' of the M hyorhinis contaminant. Re-infection of these cells with an exogenous strain of M hyorhinis resulted in the same cell detachment effect, and this strain when labeled with [3H]uridine also sedimented at a density of 1.18 g/cm3. The salient feature of these studies is that M hyorhinis sediments at the same density of mouse mammary tumor virus (MMTV) in sucrose density gradients. This was demonstrated by sucrose density gradient analyses of a purified sample of MMTV, assaying for reverse transcriptase activity, and a [3H]uridine labeled sample of the M hyorhinis present in the MT cell cultures. (Author abstract) (21 Refs)

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VIRUS ISOLATION AND CHARACTERIZATION

1. TYPE C VIRUS PARTICLES IN A CORD T-CELL LINE DERIVED BY CO-CULTIVATING NORMAL CORD LEUKOCYTES AND HUMAN LEUKAEMIC T CELLS.

Miyoshi I, Kubonishi I, Yoshimoto S, Akagi T, Ohtsuki Y, Shiraishi Y, Nagata K, Hinuma Y
Dept. Medicine, Kochi Medical Sch., Kochi 781-51, Japan
Nature; 294(5843):770-771 1981

Cocultivation of adult T-cell leukemia (ATL) cells with cord WBC from a male infant was used to establish a T-cell line that expresses ATL-associated antigens (ATLAs) and contains numerous C-type virus particles. The ATLAs were detected by indirect immunofluorescence using ATL patients' sera and fluorescein isothiocyanate-conjugated goat antihuman IgG. Thin-section electron microscopy revealed the virus particles, which are predominantly mature and consist of an electron-dense nucleoid and an outer membrane. (8 Refs)

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VIRUS ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

2. HEMATOPOIETIC CELLS TRANSFORMED IN VITRO BY REVT AVIAN RETICULOENDOTHELIOSIS VIRUS EXPRESS CHARACTERISTICS OF VERY IMMATURE LYMPHOID CELLS.

Beug H, Muller H, Grieser S, Doederlein G, Graf T
Institut fur Virusforschung, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany
Virology; 115(2):295-309 1981

REVT (avian reticuloendotheliosis virus) is a replication defective acute leukemia virus possessing a transformation-specific sequence designated rel. Hematopoietic cells transformed by REVT in vitro expressed cell surface markers of immature B lymphocytes. Some clones of transformed cells also expressed cell surface determinants of immature T lymphocytes. An antiserum specific for REVT-transformed cells reacted with the cell surface of lymphoid leukemia cells of both the B- and T-cell lineage as well as with a subpopulation of cells in normal spleen, thymus, and bone marrow. REVT-transformed cells did not express surface or cytoplasmic immunoglobulin chains nor terminal deoxynucleotidyl transferase, nor were they susceptible to infectious bursal disease virus. As expected, they were also negative for the expression of all erythroid and myeloid differentiation parameters tested. (Author abstract) (53 Refs)

3. IDENTIFICATION OF A 20,000-DALTON PROTEIN IN SSV-TRANSFORMED NONPRODUCER CELLS.

Thiel HJ, Matthews TJ, Weinhold KJ, Broughton EM
Bundesforschungsanstalt fur Viruskrankheiten der Tiere, P.O. Box 1149 Paul Ehrilch-Strasse 28, Tubingen, W. Germany
Virology; 115(2):401-405 1981

Simian sarcoma virus-transformed nonproducer cells (SSV-NP cells) express a 20,000-dalton protein (p20), which is precipitated by an autologous antiserum against SSV-NP cells. The molecule is shed or secreted from the cells because it was found in cell extracts as well as tissue culture supernatants. P20 was detected in SSV-transformed cells from three different species, but not in helper virus (SSAV)-infected nontransformed cells. The data suggest that the expression of p20 is specific for transformation by SSV. (Author abstract) (14 Refs)

4. SIMILARITIES AND DIFFERENCES BETWEEN THE EFFECTS OF EPIDERMAL GROWTH FACTOR AND ROUS SARCOMA VIRUS.

Cooper JA, Hunter T
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
J Cell Biol; 91(3):878-883 1981

We have derived a line of A431 human tumor cells infected with Rous sarcoma virus (RSV). The infected cells contain the RSV-transforming protein, pp60src, which has characteristic tyrosine-specific protein kinase activity. As in other RSV-transformed cells, a 36,000-dalton protein is phosphorylated in RSV-infected A431 cells. Addition of epidermal growth factor (EGF) to the cells induces further ph osphorylation of this protein. In contrast, this phosphoprotein is not detected in uninfected A431 cells, except when treated with EGF. Increased phosphorylation of the EGF receptor protein and of an 81,000-dalton cellular protein is dependent upon addition of EGF to the culture fluids, in both control and RSV-infected A431 cells. The results are discussed with reference to the similarities and differences between the tyrosine-specific protein kinases induced by RSV and activated by EGF. (Author abstract) (42 Refs)

5. REVERTANTS OF RAT CELLS TRANSFORMED BY AVIAN ERYTHROBLASTOSIS VIRUS.

Quade K, Saule S, Stehelin D, Kitchener G, Hayman MJ
Div. Virology, Natl. Inst. Medical Res., Mill Hill, London NW7 1AA, England
Virology; 115(2):322-333 1981

Morphological revertants of the avian erythroblastosis virus (AEV)-transformed rat cell line AT1a were isolated and characterized. The revertants are similar to the uninfected parental rat cell line in that they have regained an organized cytoskeleton and they are no longer capable of anchorage-independent growth. The pattern of integrated viral DNA in the revertants is indistinguishable from that of the transformed parent. However, the revertants do not express the integrated viral genome at either the mRNA or protein level. Phenotypic reversion thus is probably due to reduced transcription of the AEV-transforming gene below a threshold necessary to induce morphological transformation. (Author abstract) (45 Refs)

6. ALTERATIONS IN ELECTROPHYSIOLOGY OF CULTURED BALB/CFC3H MOUSE MAMMARY EPITHELIUM ASSOCIATED WITH NEOPLASTIC TRANSFORMATION.

Bisbee CA
NIH, Room 6N-307, Building 10, Bethesda, MD, 20205
Cancer Lett; 14(3):237-242 1981

Prolactin-controlled transepithelial electrophysiological properties associated with the neoplastic state and with the presence of mammary tumor virus in BALB/cfC3H mouse mammary epithelium are described. Short-circuit current values from tumor-cell cultures were observed to be max 20% of prelactating cell culture values. Neoplastic epithelium potential differences were only slightly lower than in prelactating epithelium. Resistances of tumor-cell cultures were not different from those of prelactating cell cultures. The findings suggest a reduction in prolactin sensitivity with expression of mammary tumor virus. Such decreased prolactin sensitivity may result from differential effects of prolactin on the component elements of short-circuit current and resistance. (31 Refs)

VIRUS REPLICATION AND EXPRESSION

7. INCORPORATION OF INFLUENZA VIRUS ANTIGENS IN AVIAN SARCOMA VIRUS ENVELOPE.

Migunova BV, Kuznetsov OK
Res. Inst. of Vaccines and Sera, USSR Ministry Health, Leningrad, USSR
Vopr Onkol; 27(10):63-67 1981

The mixture of influenza virus and pseudotype of Rous sarcoma virus RSV (PAB-A) grown in chick embryos or cell culture of chick fibroblasts produces a progeny which can be partially neutralized by a heterologous immune serum. The fraction of viral particles, the transformation activity of which is susceptible to suppression by both homologous anti-RSV (PAB-A) and heterologous serum, immune to influenza virus, amounts to approximately 20%. After passage, these particles lose this property which suggests a non-genetic character of the phenomenon. Hence, dual infection results in phenotypic mixing and formation of particles with nucleoprotein of RSV (PAS-A) which contain antigens of avian sarcoma and influenza viruses in their envelopes. (Author abstract) (8 Refs) (In RUS)

GENETICS

8. SPONTANEOUS LYMPHOMAS IN SJL/J-(V+) MICE: ECOTROPIC AND DUALTROPIC VIRUS EXPRESSION IN NORMAL AND LYMPHOMATOUS TISSUES.

De Rossi A, D'Andrea E, Colombatti A, Fischinger PJ, Chieco-Bianchi L
(c/o Chieco-Bianchi) Lab. Oncology, Inst. Pathological Anatomy, Univ. Padova, Via Gabelli 61, 35100 Padova, Italy
JNCI; 67(6):1241-1250 1981

Approx 60% of inbred SJL/J-(v+) adult mice having high levels of ecotropic endogenous XC+ virus showed virus activation within the first mo of life, while the others produced virus at comparable levels later on. In an attempt to correlate the time of virus activation with the incidence and latency of lymphomas, the tails of 57 1-and 2-mo-old mice were tested for virus presence, and the mice were then observed for lymphoma appearance. While all 2-mo-old mice expressed ecotropic virus, only 63% of the 1-mo-old mice were virus-positive. However, no relationship existed between early virus production (within 1 mo) or late virus production and lymphoma latency, total lymphoma incidence, and histopathology. In contrast with high titers of XC+ virus in tail tissues of diseased mice, a markedly low virus content was found in lymphomatous organs. This difference was not due to selective growth of poor virus-producer cells or to inhibitory factors possibly released by the inflammatory cell component. Viral protein content and XC+ virus titer were not closely correlated in the neoplastic organs. Search for XC- viruses revealed that only 1 of 6 aged normal and 16 of 19 lymphomatous mice produced viruses that grew on mink lung cells. By use of a standard limiting dilution cloning procedure, four isolates were obtained that showed tropism for both murine and heterologous cells. Three of these isolates induced cytopathic changes similar to those induced by MCF viruses on mink lung cells but not on mouse cells. Interference and neutralization assays performed to better characterize the virus envelope properties further indicated that SJL/J isolates had features typical of MCF dualtropic viruses. (Author abstract) (67 Refs)

9. ROLE OF THE B COMPLEX IN THE GENETIC CONTROL OF ROUS SARCOMA VIRUS INDUCED TUMOR S IN CHICKENS.

Gebriel GM
Iowa State University, Iowa City, IA
Diss Abstr Int [B]; 42(5):1750-B 1981

Eight highly inbred lines, with inbreeding coefficients ranging from 81% to 97% and segregating for eight different B complex alleles were used in this study. Also included were two moderately inbred (40%) heavy-breed lines and one outbred Leghorn line segregating for the blood group alleles, B1, B2 and B19. Birds were blood-typed for B locus alloantigens at 5 wk of age. Each genetic group was challenged with Rous sarcoma virus subgroups A, B and C. Tests were based on both wing web-challenge (WWC) on 5-wk-old chicks and on the chorioallantoic membranes of 12-day embryos (CAM) test. These results indicate that the B complex-linked genes, controlling tumor expression, belong to a multiple allelic series at a single B complex-linked locus. In addition, the results from both the WWC and CAM test support the findings that the tv loci for cellular resistance maps outside the B complex. Also, the statistical evidence verifies the earlier findings that tva and tvc loci are linked. As expected, most of the variation in tumor regression in susceptible birds was linked to the B complex. Thus part of the genetic variation in tumor regression may be controlled outside the B complex. Genes coding for control of the fate of Rous sarcoma virus subgroup A induced tumors are evidently closely linked to the locus controlling immune response to GAT. The latter maps within the Ir region of the B histocompatibility complex. These findings are important as possible criteria for detecting and selecting disease-resistant fowl. (no Refs)

IMMUNOLOGICAL STUDIES

10. T CELL RECOGNITION OF MOLONEY LEUKEMIA VIRUS PROTEINS: III. T CELL PROLIFERATIVE RESPONSES AGAINST GP70 ARE ASSOCIATED WITH THE PRODUCTION OF A LYMPHOKINE INDUCING 20 ALPHA-HYDROXYSTEROID DEHYDROGENASE IN SPLENIC LYMPHOCYTES.

Ihle JN, Lee JC, Rebar L
Biological Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
J Immunol; 127(6):2565-2570 1981

One of the characteristic cellular immune responses associated with the regression of Moloney leukemia/sarcoma virus-induced tumors is a T cell proliferative response against the major viral envelope glycoprotein, gp70. The results described here demonstrate that associated with this proliferative response is the production of a lymphokine, Interleukin 3 (IL-3). The production of IL-3 was immunologically specific and showed the same specificity as that observed in blastogenic responses. IL-3 production was dependent upon an antigen-specific Thy-1.2+, Lyt-1+, 2-lymphocyte subpopulation but did not require the presence of an Ia+ or an adherent accessory cell. The results also suggested that IL-3 may constitute one of the blastogenic factors previously shown to be involved in the proliferative response to gp70. I n particular purified IL-3 was found to induce proliferation of both normal and immune nylon wool purified splenic lymphocytes. The phenotype of the responding lymphocyte subpopulation was Thy-1.2-, Lyt-1-, 2-, Ig-, and Ia-. Maximal IL-3 production occurred approximately 48 hr after the addition of antigen and its production was significantly blocked by mitomycin C. These characteristics were unlike those for the general production of blastogenic factor activity suggesting that IL-3 is responsible for only a minor component of the proliferative response. (Author abstract) (19 Refs)

11. ACCESSORY CELLS IN THE IN VITRO GENERATION OF TYPE C VIRUS-SPECIFIC T KILLER LYMPHOCYTES: II. DEMONSTRATION OF A T HELPER CELL IN THE SPLEEN OF IN VIVO PRIMED MICE.

Gomard E, Wybier-Franqui J, Simmler MC, McKenzie IF, Levy JP
Laboratoire Immunologie et Virologie des Tumeurs, INSERM U 152, ERA 781, Hopital Cochin 27, rue du Faubourg Saint Jacques, 75645 Paris Cedex 14, France
J Immunol; 127(6):2291-2295 1981

The existence of a helper T cell cooperating with cytolytic T lymphocytes (CTL) in cell-mediated anti-tumor responses specific for the virus-induced FMR antigens can be demonstrated by using unprimed thymocytes as CTL precursors and in vivo primed irradiated spleen cells as helper. The helper T cells express Thy-1.2 and Lyt-1.2 antigens at their surface, but not Lyt-2.2. The helper function required the presence of macrophages to be detected, is antigen specific, and appears unusually radiosensitive compared with previously described helper T cell function. (Author abstract) (27 Refs)

12. AGE- AND SEX-RELATED DIFFERENCES IN ANTIBODY FORMATION AND BLASTOGENIC RESPONSIVENESS OF SPLENOCYTES FROM RIII MICE DEVELOPING VIRUS-INDUCED MAMMARY ADENOCARCINOMA.

Specter S, Friedman H
Dept. Medical Microbiology and Immunology, Univ. South Florida Coll. Medicine, Box 10, 12901 North 30th St., Tampa, FL, 33612
JNCI; 67(6):1347-1351 1981

Inbred RIII mice, known to be infected neonatally with murine mammary tumor virus so that females develop mammary adenocarcinoma by 12-15 mo of age, were examined with regard to antisheep red blood cell antibody responses at the cellular level. Female mice, 3-11 mo old, compared to male mice of the same ages had consistent and significant depression of the antibody response of their splenocytes. Furthermore, female mice with adenocarcinoma showed an even greater depression of the antibody response. Spleen sizes were consistently increased in females as compared to those of male mice throughout the first yr of life. The blastogenic responsiveness of the splenocytes to the B-cell mitogen Escherichia coli lipopolysaccharide and the T-cell mitogen phytohemagglutinin-P was not significantly different between male and female mice during the same periods, although the responses of the older tumor-bearing female mice to phytohemagglutinin-P were lower than those of non-tumor-bearing female mice. A complex relationship between age, sex, and immune responsiveness was evident in these mammary tumor virus-infected mice, which made it difficult to attribute a specific immune event to emergence of the mammary adenocarcinomas in the female as compared to male mice. (Author abstract) (9 Refs)

13. STUDIES ON INTERACTIONS BETWEEN PLASMINOGEN ACTIVATOR-CONTAINING FLUIDS AND AVIAN AND MURINE LYMPHOCYTES.

Wainberg MA, Cohen SD
Lady Davis Inst. for Medical Res., Sir Mortimer B. Davis Jewish General Hosp., Montreal, Quebec, Canada
Dev Comp Immunol; 5(4):649-660 1981

The ability of plasminogen activator (PA) from culture fluids of avian virus (AVS)-transformed chicken embryo fibroblasts (CEF) and avian sarcoma cells to serve as a lymphocyte mitogen and to modulate lymphocyte response was studied. High levels of PA and fibrinolytic activity were associated with both types of tumor cells induced by ASV. Tumor levels were 1.5-8x greater than than those of ASV-transformed CEF. Of 10 culture fluids, 2 from normal and 8 from ASV-transformed CEF cells, 9 possessed non-specific mitogenic capacity. No mitogenesis was associated with 2/2 cultures from normal CEF cells and with 3/8 cultures from ASV-transformed CEF cells. These latter preparations contained little or no demonstrable PA activity. Both papain and trypsin were stimulatory to avian lymphocytes within a narrow range of concentrations. Non-specific mitogenesis of Balb/c mouse splenic lymphocytes could only be effected by those culture fluids which contained significant levels of PA activity. Urokinase was also mitogenic for mouse lymphocytes. The inhibition of mitogenesis by PA antagonists was examined. Results of studies of the immunomodulating effects of culture fluids and urokinase suggested that the mitogenic effect of PA may be dependent on cofactors. Circumstantial evidence that PA may act as a lymphocyte mitogen was provided. (17 Refs)

14. IMMUNOPOTENTIATING ACTION OF STREPTOCOCCAL PREPARATION OK-432 AND PROTEIN-BOUND POLYSACCHARIDE PS-K ON DEPRESSED STATE OF CELL-MEDIATED AND HUMORAL IMMUNITIES OF FRIEND LEUKEMIA VIRUS INFECTED MICE.

Kiyohashi A
Dept. Internal Medicine, Sch. Medicine, Kitasato Univ., Japan
Nippon Gan Chiryo Gakkai Shi; 16(4):641-646 1981

The effects of OK-432, a penicillin-treated Group A hemolytic streptococci, and PS-K, a protein-bound polysaccharide, on the immune response of male ICR and ddY mice infected with Friend leukemia virus (FLV) were examined. FLV-infected mice were injected iv with either 0.5 KE (1 KE = 0.1 mg lyophilized streptococci) OK-432 or 30 mg/kg PS-K daily for 3 consecutive days, from 5 days before and from 3 days after FLV inoculation. Lymph node cells of mice treated with both FLV and OK-432 responded well to ovalbumin (OA) and purified protein tuberculin derivative in macrophage migration inhibition tests conducted 21-31 days after immunization with OA. Mice treated wtih FLV and PS-K showed no response. Both response of hemolytic plaque forming cells to sheep RBC (anti-SRBC PFC) and serum antibody production were not detected in the FLV-infected mice, whether injected with OK-432 or PS-K. The anti-SRBC PFC response and antibody production in OK-432-treated mice were slightly greater than those in the other FLV-infected groups, but the differences were not significant. The results suggested that OK-432 has an immunopotentiating activity on the depressed state of cell-mediated immunity, while PS-K does not. Neither PS-K nor OK-432 enhanced humoral immunity in FLV-infected mice. (13 Refs)

OTHER RELATED STUDIES

15. GROWTH AND INFECTIVITY TITRATION OF VIRULENT INFECTIOUS BURSAL DISEASE VIRUS IN ESTABLISHED CELL LINES FROM LYMPHOID LEUKOSIS TUMORS.

Yamaguchi S, Imada T, Kawamura H

Poultry Disease Lab., Natl. Inst. Animal Health, 4909-58 Kurachi, Seki, Gifu, 501-32, Japan

Avian Dis; 25(4):927-935 1981

The most suitable cell culture for growth of virulent infectious bursal disease virus (IBDV) was investigated as was the possibility of infectivity titration and serological tests with cell cultures. In the study of susceptibility to the virulent (wild) and attenuated IBDV by detection of fluorescent antigen in inoculated cells, lymphoblastoid cell lines LSCC-BK3 (LBK) and LSCC-CU10 were susceptible to both, while line LSCC-1104-B-1 was susceptible only to the attenuated form. The LBK line was the most susceptible line to any IBDV and was used in further experiments. Two lymphoid leukosis and two MD cell lines were refractory to growth of any type of IBDV. When the J1 strain of virulent IBDV was inoculated into LBK cells, intra- and extracellular viruses began logarithmic increase between 4 and 8 hr postinoculation and reached 106.3-7.3 TCD50/0.1 ml, respectively, at 72 hr. Infectivity titration and serum-neutralization tests of virulent IBDV were possible with LBK cells. (13 Refs)

16. THE IMMUNOREGULATORY CHARACTERISTICS OF THE LACTIC DEHYDROGENASE VIRUS (LDV), A COMMON CONTAMINANT OF TUMORS.

Isakov N, Segal S, Feldman M
Dept. Cell Biology, Weizmann Inst. Science, Rehovot, Israel
Cell Mol Biol; 27(2/3):83-96 1981

A tumor-enhancing and antibody increasing spleen cell-associated factor originating in Lewis lung carcinoma (3LL)-bearing C57BL/6 mice was identified as the lactic dehydrogenase virus (LDV). A potent immunoregulating factor was obtained only following the inoculation of LDV-infected but not LDV-free tumor cells. The observed augmentation of humoral responses by an acute infection with LDV was found to be fully correlated with the ability of the virus to replicate and establish a persisting infection in the host. LDV caused an augmented humoral response in all mouse strains tested (causing a life-long viremia), but failed to influence the humoral response in rats, which are an LDV-resistant species. We found that although an infection with LDV causes a polyclonal B-cell activation it does not affect all of the different B-cell clones and in the presence of a specific antigenic stimulus it preferentially triggers the IgG2 subclass of antibody-secreting B cells. An acute LDV infection causes a substantial suppression of cell-mediated immunity functions and a delayed thyroid allograft rejection was demonstrated in infected mice. Since mononuclear phagocytes, which are the target cells of LDV, play an important role in cellular immune responses, we tested the immunogenic antigen-presenting capacity of LDV-infected macrophages, using a system in which in vitro reactivation of memory T cells is dependent upon effective specific antigen presentation by macrophages. We found that the antigen presentation capacity of macrophages from acute LDV-infected mice is impaired. These results may contribute to a better understanding of the ways in which mammalian RNA viruses may act as immunomodulators. (Author abstract) (42 Refs)

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VIRUS ISOLATION AND CHARACTERIZATION

1. TRANSFORMATION OF NORMAL HUMAN CORD LYMPHOCYTES BY CO-CULTIVATION WITH A LETHALLY IRRADIATED HUMAN T-CELL LINE CARRYING TYPE C VIRUS PARTICLES.

Miyoshi I, Yoshimoto S, Taguchi H, Ohtsuki Y, Kubonishi I, Shiraishi Y, Akagi T

Dept. Anataomy, Kochi Medical Sch., Oko-cho, Nankoku-shi, Kochi-ken 781-51, Japan

Gan; 72(6):997-998 1981

Normal human cord WBC were co-cultured with lethally irradiated MT-2 cells to produce a T-cell line of cord WBC origin which harbored type C virus particles and adult T-cell leukemia-associated antigens (ATLA). On the 11th day of culture, 1 x 10(6) lethally x-irradiated (6,000 R) MT-2 cells were added to two of four dishes of cord WBC. Control cultures included two dishes of irradiated MT-2 cells without cord WBC and two dishes of cord WBC alone. All cultures were incubated at 37 C in a humidified 7.5% CO2 atmosphere. Two wk after co-culture, scattered foci of cell aggregates were observed on the sheets of macrophages. Continuous growth of cells developed in two of the co-cultured dishes, and this cell line, designated Ok, was maintained in culture for 3 mo. The Ok line consisted of mostly immature lymphoid cells with multinucleate giant cells. Sixty-six percent of the Ok cells formed spontaneous rosettes with neuraminidase-treated sheep RBC. Most of the Ok cells were positive for Leu-1 and OK11, but negative for Leu-2a and Leu-3a. None of the 145 Ok cells studied contained a Y chromosome; 41/46 cells had a 46,XX karyotype. Electron microscopy revealed many type C virus particles in the extracellular spaces. Most of the Ok cells were positive for ATLA when reacted with ATL patient's sera. The cultured cells gave a positive reaction with five sera from ATL patients but not with five sera from normal control individuals. These findings suggest that the type C virus was apparently transmitted from the MT-2 cells to the cord lymphocytes during co-cultivation. (8 Refs)

VIRUS ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

2. DIAGNOSIS OF PRIMARY BREAST CARCINOMA THROUGH IMMUNOHISTOCHEMICAL DETECTION OF ANTIGEN RELATED TO MOUSE MAMMARY TUMOR VIRUS IN METASTATIC LESIONS: A REPORT OF TWO CASES.

Mesa-Tejada R, Oster MW, Fenoglio CM, Magidson J, Spiegelman S
Inst. Cancer Res., 701 West 168th St., New York, NY, 10032
Cancer; 49(2):261-268 1982

Recent investigations have established that approximately half of human breast carcinomas contain an immunohistochemically detectable antigen which is cross-reactive with the 52,000-dalton major glycoprotein (gp52) of the mouse mammary tumor virus (MMTV). This antigen can be localized in paraffin-embedded sections of routinely fixed tissues using heterologous antibodies to gp52 or MMTV. This report describes two patients with metastatic carcinoma in axillary lymph nodes without any clinical evidence of a primary lesion in the breast or elsewhere. The localization of the gp52-related antigen in paraffin-embedded sections of both metastatic lesions suggested the presence of primary mammary carcinoma. In both instances, this suggestion was ultimately confirmed by the finding of primary lesions in which the gp52-related antigen was also found. (Author abstract) (30 Refs)

3. EARLIER APPEARANCE OF MURINE MAMMARY TUMOR VIRUS-ASSOCIATED ANTIGENS IN DUCT-ALVEOLUS NODULES INDUCED BY TRANSPLANTATION OF FETAL SALIVARY MESENCHYME INTO C3H MOUSE MAMMARY GLANDS.

Sakaguchi S, Takahashi T, Sakakura T, Sakagami Y, Nishizuka Y, Tanaka H
(c/o Takahashi) Lab. Experimental Pathology, Aichi Cancer Center Res. Inst., Tashiro-cho, Chikusa-ku, Nagoya 464, Japan
Gan; 72(6):982-987 1981

Mammary epithelium of adult C3H mice in contact with fetal salivary mesenchyme took morphogenetically a salivary gland-like pattern of growth and developed a hyperplastic nodular mass at the site of transplantation. When murine mammary tumor virus-bearing C3H mice were treated in this way, early development and high incidence of mammary cancer were observed from these nodules compared to unstimulated mammary glands of the same host. Since it is known that murine mammary tumor virus plays a major role in mammary tumor development, the viral antigens in these hyperplastic nodules were examined by means of the immunofluorescence technique. As early as 2 wk after mesenchyme transplantation, the antigens were observed in the ductular or alveolar structure of these nodules, while surrounding normal tissues were not stained. Positive fluorescence was also observed in the mammary tumors that developed from these stimulated nodules. These results strongly suggested the involvement of murine mammary tumor virus in the early development of mammary cancer induced by fetal mesenchyme transplantation. (Author abstract) (12 Refs)

4. ENDOGENOUS MULV INFECTION DOES NOT CONTRIBUTE TO ONSET OF RADIATION- OR CARCINOGEN-INDUCED MURINE THYMOMA.

Mayer A, Dorsch-Hasler K
Dept. Pathology, New York Univ. Sch. Medicine, 550 First Ave., New York, NY, 10016
Nature; 295(5846):253-255 1982

The contribution of endogenous murine leukemia virus (MuLV) to onset of radiation- or carcinogen-induced murine thymoma was examined. The effect of cellular Fv-1 locus on the development of radiation-induced thymic lymphoma was tested to determine whether this form of induced thymoma also requires active MuLV infection. RF/J and BALB/cJ strains of mice were highly susceptible to radiation induction of thymoma. To measure the effect of Fv-1 more directly, the incidence of radiation-induced thymoma was determined in (BALB/c x RF)F1 x RF backcross mice typed for the alleles carried at the Fv-1 locus. Fv-1n homozygous and Fv-1n/Fv-1b heterozygous backcross mice were identified by typing each backcross mouse for its phenotype at the Gpd-1 locus, which is closely linked to the Fv-1 locus. The two subpopulations of the backcross did not differ substantially in radiation-induced thymoma incidences. The finding are not consistent with a requirement for active infection by endogenous MuLV in the development of radiation-induced thymoma. When the backcross mice were typed for their haplotype at H-2, no H-2-associated effect was observed to influence relative resistance to radiation-induced thymoma. RF and 129 mice were chosen for induction of thymoma by N-nitrosomethylurea. Both strains showed high sensitivity. RF mice are much more sensitive to radiation-induced thymoma than 129 mice. F1 hybrid mice also developed a high incidence of the tumor. These finding s indicate a basic difference between the etiologies of spontaneous and carcinogen- or radiation-induced thymoma. Spontaneous occurrence of the tumor is associated with expression of endogenous mouse-infectious MuLV activities, including both XC-positive and XC-negative ecotropic MuLV and dualtropic MCF MuLV. Active infection of cells by endogenous MuLV is not essential to development of thymic lymphoma in the mouse following exposure to radiation or chemical carcinogens. (23 Refs)

5. ORGANIZATION AND REORGANIZATION OF IMMUNOGLOBULIN GENES IN A-MULV-TRANSFORMED CELLS: REARRANGEMENT OF HEAVY BUT NOT LIGHT CHAIN GENES.

Alt F, Rosenberg N, Lewis S, Thomas E, Baltimore D
Center Cancer Res., Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139
Cell; 27(2):381-390 1981

The structure of immunoglobulin-related genes was analyzed in individual Abelson murine leukemia virus (A-MuLV)-transformed lymphoid cell lines. Essentially all of these lines, whether immunoglobulin-containing or null, had DNA rearrangements in the vicinity of the JH regions on both chromosomes as well as deletions of at least 5 kb of DNA 5' to JH. None of these lines, however, except rare light chain producers had detectable rearrangements at either their kappa or lambda light chain loci. In contrast to A-MuLV-transformants derived from bone marrow, those from early fetal liver frequently contained more than 2 and sometimes 12 or more distinct, rearranged JH-containing fragments. Cellular subclones derived from these lines had a subset, usually two, of the fragments found in the parent line. Therefore, heavy chain gene rearrangement appears to precede that of light chain gene rearrangement and is still continuing in certain cultured A-MuLV transformants. (Author abstract) (43 Refs)

6. PROGRAMMED AND ALEATORY ELEMENTS IN THYMIC LEUKEMIA.

Tempelis LD, Zielinski CC, Waksal SD, Khiroya RH, Schwartz RS, Martin WJ, Bach FH, Alexander
Winter Res. Lab., Mount Sinai Medical Center, Milwaukie, WI, 53201
Transplant Proc; 13(4):1854-1857 1981

A study was undertaken to test whether thymocytes that possess receptors for the viral envelope glycoprotein gp70 of a given thymotropic leukemogenic virus are the target cells for leukemogenic transformation by that particular virus. Thymocytes derived from control mice showed a consistently similar pattern: a high expression of Thy-1.2, Lyt-1, and Lyt-2, and a low expression of H-2Kk and Iak. Receptors for peanut agglutinin were uniformly present in high percentages. Moloney virus (MuLV) antigen expression was low on thymocytes derived from control mice. Each tumor had a distinctive phenotype. All phenotypes were positive for Thy-1.2 and MuLV antigen. The thymocytes from thymomas induced by each cloned polytropic retrovirus (PTV) presented uniformly with a stable phenotype characteristic of that particular PTV clone. The percentage of MuLV-expressing thymocytes was high. Thymocytes from CBA and HRS mice 4, 6, and 12 wk after injection with PTV 1 and PTV 2 were analyzed for an immediate effect on the thymocyte phenotype. The phenotype of thymocytes derived from these mice was not changed drastically compared to uninjected control mice. Results indicate that the surface phenotype of thymocytes from spontaneously occurring thymomas is random. (9 Refs)

7. CHARACTERIZATION OF A BONE MARROW CELL LINE TRANSFORMED BY ABELSON'S MURINE LEUKEMIA VIRUS.

Pinter A, Borzsonyi M
Orszagos Kozegeszsegugyi Intezet, Budapest, Hungary
Magy Onkol; 25(4):217-226 1981

Development of transformed cell line (Gr 17) was observed after infection of a long-term bone marrow cell culture from BALB/c mice with Abelson's murine leukemia virus (strain P 160) (A-MuLV). According to their phenotype, the Gr 17 cells corresponded to the early maturation form of B lymphoid cells (pre-B lymphoblasts). The results of the tests for alpha-naphthylacetate esterase, Hb, phagocytosis, and membrane surface Ig were negative, but cytoplasmic IgM was found. In contrast to the hitherto described cell lines obtained by transformation with A-MuLV, hypodiploid chromosome set and the presence of metacentric chromosome due to translocation were observed. Development of thymus-independent generalized lymphoma was observed after transplantation of Gr 17 cells (2 x 10(7) cells iv) in 4-6-wk-old male and female BALB/c mice. The take rates were 9/10 in the females and 8/10 in the males. The mean latent periods were 41 days in the females and 50 days in the males. Typical Abelson's tumors were induced by the virus produced by the cell line in newborn BALB/c mice. (27 Refs) (In HUN)

8. H-2D CONTROL OF RADIATION LEUKEMIA VIRUS INDUCED NEOPLASIA: EVIDENCE FOR INTERACTION OF VIRAL AND H-2 GENOMIC INFORMATION.

Meruelo D, Kramer J, Uhr JW, Festenstein H, Elkins W, Dutton RW, Ferrone S
Irvingtone House Inst., Dept. Pathology, New York Medical Center, 550 First Ave., New York, NY, 10016
Transplant Proc; 13(4):1858-1862 1981

Integration of viral genetic information occuring at or near H-2D and resulting in deregulation of transcription of H-2D genes, as the possible mechanism by which radiation leukemia virus (RadLV) infection increases H-2D expression in the thymus, is discussed. Intrathymic inoculation of RadLV to mice in varied genotypes leads to increased H-2D expression as long as their genotype is Fv-1b. The inductive mechanism augmenting H-2Dd synthesis does not operate in a trans mode. Thymocytes from susceptible and resistant mice were exposed to particular agents in vivo. No agent, except soluble extracts from RadLV-infected thymocytes, was capable of selectively changing H-2D antigen expression on thymocytes of resistant but not susceptible mice. Blocking virus integration prevents RadLV-induced changes in H-2D expression. Experiments showed that ethidium bromide and fluoro-deoxyuridine (FUdR) inhibit H-2D antigen deregulation, while thymidine is able to block the effects of FudR. RadLV is able to induce H-2D increases as early as 12 hr after inoculation. The integration of proviral DNA into host genomic material requires a minimum of 6 hr. The inability of soluble extract from resistant thymocytes older than 3-5 wk past RadLV infection to increase H-2D expression vs the fact that in resistant mice H-2D remains elevated for at least 12 wk after virus infection implies that the virus-coded information once integrated can continue to deregulate H-2D antigen expression even in the absence of provirus synthesis. (14 Refs)

9. HERITABLE DIFFERENCES AMONG GP70-LIKE MOLECULES ON C3H ULTRAVIOLET LIGHT-INDUCED FIBROSARCOMAS.

Roman JM, Hirsch J, Readhead C, Levy D, DeOgny L, Dreyer WJ, Lennox ES, Rogers MJ, Alexander P, Ferrone S
Dept. Biology, California Inst. Technology, Pasadena, CA
Transplant Proc; 13(4):1782-1786 1981

Tumor antigens found on UV-induced fibrosarcomas (UV-FS) in C3H mice were studied. C3H/HeN mice were immunized with UV-FS cells implanted by trocar. Syngeneic antisera (AS) were obtained from the mice. The AS contained antibodies (AB) specific for the immunizing tumor and AB that cross-reacted with other C3H FS lines. Immunoprecipitation of 125I-labeled lysates of six different UV-FS lines detected the consistent presence only of molecules of mol wt 70,000-90,000 dalton. Although resolution of the complexity of the molecules was not possible with one-dimensional gel electrophoresis (GE), two-dimensional GE showed that the tumor molecules recognized by the AS had heterogeneous charges and heterogeneous mol wt. Heterogeneity was possible due to variations in glycosylation, amino acid sequences, or proteolytic processing of precursor molecules. Molecules apparently identical to those precipitated by syngeneic AS were precipitated by goat anti-Rauscher leukemia virus gp70 and goat anti-BALB/c virus-2 gp70 sera. Within a tumor cell line the patterns of heterogeneous molecules in the 70,000-90,000 mol wt range were constant and independent of in vivo or in vitro passage generation. Among various tumor lines considerable variations were apparent. Analysis of molecules from UV-FS suggests that the tumors produce at least two distinct gp70-like molecules, one that is the C3H ecotropic viral gp70 , and one of lower mol wt that is substantially different from ecotropic gp70. (20 Refs)

10. MOLECULAR MECHANISMS INVOLVED IN MORPHOLOGICAL VARIATION OF AVIAN SARCOMA VIRUS-INFECTED RAT CELLS.

Chiswell DJ, Enrietto PJ, Evans S, Quade K, Wyke JA
(c/o Wyke), Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England
Virology; 116(2):428-440 1982

Clones of avian sarcoma virus (ASV)-infected rat cells are heterogeneous, containing both morphologically transformed and morphologically normal cells. Morphological variation is reversible: normal cells can give rise to transformed daughters and they in turn can segregate morphologically normal revertants. However, reversion of transformed clones seems to occur more readily than transformation of normal cells. In most cases, morphologically normal cells contain recoverable viruses with no defect in transformation and yet the cells themselves are usually fully susceptible to transformation by superinfecting ASV. With one exception, morphological changes are not accompanied by detectable alterations in the size or chromosomal location of the single ASV provirus that these clones possess. In one clone, A11, that has been examined in detail, transformed segregants contain virus specific RNAs and the viral transforming protein, pp60src, whereas in normal subclones neither RNA nor protein can be detected. These results indicate that morphological variation reflects a reversible modulation in expression of viral functions, probably specific to individual proviruses and probably operating at the level of viral RNA transcription. (Author abstract) (33 Refs)

11. MITOCHONDRIA ARE ASSOCIATED WITH MICROTUBULES AND NOT WITH INTERMEDIATE FILAMENTS IN CULTURED FIBROBLASTS.

Ball EH, Singer SJ
Dept. Biochemistry, Univ. Western Ontario, London, Ontario, Canada
Proc Natl Acad Sci USA; 79(1):123-126 1982

Triple-immunofluorescence experiments with antibodies to cytochrome c oxidase, tubulin and vimentin have been used to immunolabel the mitochondria, microtubules, and intermediate filaments inside the same cultured fibroblasts. In particular, fibroblasts were immunolabeled after they had either been transformed by infection with Rous sarcoma virus or given long-term treatment with cycloheximide. These treatments induced redistribution of the intermediate filaments into a perinuclear arrangement, segregated away from the microtubules, which remained extended to the cell periphery. In such cells, many labeled mitochondria were observed to be codistributed with the peripherally located microtubules. From these results, we infer that an association, probably involving some type of chemical linkage(s), between mitochondria and microtubules exists in these cells that is independent of the intermediate filaments. (Author abstract) (20 Refs)

12. IN VITRO DIFFERENTIATION OF CHICKEN EMBRYO SKIN CELLS TRANSFORMED BY ROUS SARCOMA VIRUS.

Yoshimura M, Iwasaki Y, Kaji A

(c/o Kaji) Dept. Microbiology, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA, 19017

J Cell Physiol; 109(3):373-385 1981

Epidermal cells isolated from 14-day chicken embryo shank skin epidermis were infected in vitro with Rous sarcoma virus (RSV). After a few wk, rapidly growing colonies of epithelial cells appeared among transformed fibroblastic cells. When isolated and subcultured, the cells possessed typical markers of skin epidermis such as major keratin and typical epithelial cell type morphology which strongly suggested they were transformed epidermal cells which retained their differentiated characteristics but had the capacity to propagate in cell culture. If cells infected with RSV tsNY68 (a mutant with a temperature lesion on the src gene) were used, similar transformed cells were obtained at the permissive temperature of 36 C, as evidenced by incorporation of 35S-methionine into keratins, demonstrated with polyacrylamide gel electrophoresis. At a nonpermissive temperature (41 C), appearance of cells changed, but additional keratin species were produced. Cells also developed a 'cornified envelope' which indicated extensive differentiation. The study indicates the src gene is essential for propagation of differentiated cells in culture, but eliminates only some of the differentiated characteristics. (34 Refs)

13. PLATELET-DERIVED GROWTH FACTOR (PDGF) ENHANCES THE GROWTH OF MOLONEY SARCOMA VIRUS-INDUCED TUMORS IN MICE.

Inglot AD, Inglot O

Lab. Tumor Virology, Dept. Tumor Immunology, Inst. Immunology and Experimental Therapy, Polish Acad. Sciences, Czerska 12, 53-114 Wroclaw, Poland

Arch Immunol Ther Exp (Warsz); 29(4):431-437 1981

The intramuscular (im) administration of bovine or human platelet derived growth factor (PDGF) had a marked potentiating effect on the growth of Moloney sarcoma virus (MSV)-induced tumors in BALB/c mice. PDGF had the tumor-promoting-activity when administered im on the side of inoculation of MSV 2 days after the virus, and subsequently every 2nd day for 2-3 wk. The extent of MSV-induced tumor promoting activity of PDGF was age and sex-related. In view of the recently described antagonism in action between growth factors and interferons it is suggested that both families of hormones play an important role in controlling the neoplastic proliferation. (Author abstract) (16 Refs)

14. IDENTIFICATION OF A 39,000-DALTON PROTEIN IN CELLS TRANSFORMED BY THE FBJ MURINE OSTEOSARCOMA VIRUS.

Curran T, Teich NM

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Virology; 116(1):221-235 1982

Two components of the FBJ murine osteosarcoma virus complex have been isolated separately in tissue culture; the FBJ murine leukemia virus (FBJ-MLV) by dilution and the FBJ murine sarcoma virus (FBJ-MSV) by the establishment of nonproducer transformed rat cells. Analysis of these cells using MLV antisera indicated that there were no new proteins related to viral structural proteins specifically associated with the presence of the FBJ-MSV genome. The FBJ-MSV nonproducer cells were used to induce tumors in syngeneic and allogeneic F1 rats. Sera from tumor-bearing rats were examined for activity against FBJ-MSV-specific antigens. A number of sera were found to precipitate a 39,000-dalton protein, p39, from several producer and nonproducer FBJ-MSV transformed rodent cells, but not from cells transformed by other strains of MSV or cells infected with MLV. Precipitation of p39 was not blocked by the presence of excess viral proteins, indicating that p39 is not related to the viral structural proteins. This conclusion was confirmed by methionine tryptic peptide analysis which showed that the fingerprint of p39 was distinct from those of the viral gag or env gene proteins. The data demonstrate the presence of a unique antigenic protein, unrelated to the MLV proteins, in FBJ-MSV transformed cells. (Author abstract) (41 Refs)

15. ROUS SARCOMA VIRUS-INDUCED PHOSPHORYLATION OF A 50,000-MOLECULAR WEIGHT CELLULAR PROTEIN.

Brugge JS, Darrow D

Dept. Microbiology, State Univ. New York at Stony Brook, Stony Brook, NY, 11794

Nature; 295(5846):250-253 1982

Studies were performed to determine whether the 50,000-mol wt phosphotyrosine-containing protein pp50 is present in uninfected cells and whether phosphorylation of pp50 at tyrosine depends on Rous sarcoma virus (RSV)-induced transformation. Using serum from tumor-bearing rabbits (TBR), pp50 was immunoprecipitated from 32P-labeled chicken cells transformed by the SR-A strain of RSV. Comparison of the two-dimensional gel patterns of uninfected cell phosphoproteins with a mixture of the TBR immunoprecipitate and uninfected cell phosphoproteins indicated that the pp50 which is bound to the single virus-encoded polypeptide pp60src and precipitated RSV-transformed cells migrate just to the acidic side of pp50 present in uninfected cells. Results indicate that the phosphoserine-containing form of pp50 is present in uninfected chicken cells; on transformation by RSV, a second form of pp50 detectable by two-dimensional analysis of 32P-labeled proteins contains phosphotyrosine as well as phosphoserine. The phosphorylation of pp50 at tyrosine is not temperature-sensitive (TS) in cells infected with mutant viruses containing a TS defect in the src gene. The temperature stability might result from the strong interaction between the mutant pp60src protein and pp50. (25 Refs)

16. THE LOCALIZATION OF GLIAL FIBRILLARY ACIDIC PROTEIN IN BRAIN TUMORS INDUCED IN HAMSTERS WITH AVIAN SARCOMA VIRUS.

Nakazato Y, Yamaguchi H, Takahashi K, Ishida Y
Dept. Pathology, Gunma Univ. Sch. Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371, Japan
Acta Neuropathol (Berl); 55(4):293-295 1981

The immunohistochemical localization of glial fibrillary acidic protein (GFAP) in avian sarcoma virus (ASV)-induced brain tumors was studied by the peroxidase-antiperoxidase (PAP) method in hamsters. One hundred twenty-four tumors including 54 astrocytomas, 64 pleomorphic gliomas, 5 sarcomas, and 1 unclassified tumor were stained with anti-GFAP serum. A majority of the astrocytoma cells demonstrated a positive reaction for GFAP, both in the cytoplasm and in the processes. Staining reaction of gemistocytic astrocytoma cells showed a central area of the cytoplasm stained more weakly than the peripheral zones. Bipolar spindle-shaped or small round cells in astrocytomas were negative for immunostaining. Pleomorphic glioma showed a mixed cellular composition of positive and negative staining cells. The proportion of GFAP-positive cells varied by 10-70% from tumor to tumor. Sarcomas and the unclassified tumor had a negative staining reaction. Results confirmed that a majority of ASV-induced brain tumors contain neoplastic glial cells; the findings indicated that the astrocyte is the main target cell for ASV in experimental neuro-oncogenesis. (18 Refs)

VIRUS REPLICATION AND EXPRESSION

17. GLUCOCORTICOID REGULATION OF THE HA-MUSV P21 GENE CONFERRED BY SEQUENCES FROM MOUSE MAMMARY TUMOR VIRUS.

Huang AL, Ostrowski MC, Berard D, Hager GL
Lab. Tumor Virus Genetics, NCI, Bethesda, MD, 20205
Cell; 27(2):245-255 1981

Molecular chimeras with the p21 transforming gene of Harvey murine sarcoma virus linked to DNA containing the long terminal repeat (LTR) of mouse mammary tumor virus (MMTV) have been constructed. Transformants of NIH 3T3 cells induced by transfection with MMTV LTR-p21 hybrid DNA have been identified that express the normal p21 gene product. The levels of p21 RNA and protein in these transformants are regulated by physiological concentrations of dexamethasone, a synthetic glucocorticoid hormone. Hybrid transcripts containing p21 gene sequences originate at the normal MMTV viral initiation site. It is concluded that sequences necessary for hormonal control of transcription are completely specified by the viral genome and probably map within the viral LTR. (Author abstract) (45 Refs)

18. MAMMARY TUMOR VIRUS DNA CONTAINS SEQUENCES REQUIRED FOR ITS HORMONE-REGULATED TRANSCRIPTION.

Ucker DS, Ross SR, Yamamoto KR
Dept. Biochemistry and Biophysics, Univ. California, San Francisco, San Francisco, CA, 94143
Cell; 27(2):257-266 1981

Glucocorticoids regulate the rate of transcription of integrated murine mammary tumor virus (MTV) genes in most clones of MTV-infected rat hepatoma tissue culture (HTC) cells. To determine whether hormonal regulation is mediated from flanking cellular sequences or rather from within the viral DNA, we analyzed the relative rates of transcription of MTV and adjacent HTC sequences in two lines of infected HTC cells, J2.15 and J2.17, each of which contains a single insertion of MTV DNA. In addition, we measured in uninfected HTC cells the transcriptional rates of the corresponding 'preinsertion fragments,' which may be viewed as the equivalent sequences bearing deletions of MTV DNA; the two genomic segments into which integration occurred in the two lines are unrelated. Previous work showed that glucocorticoids induce the accumulation of MTV RNA in J2.17, whereas viral transcripts are not detected in J2.15. RNA pulse-labeling experiments indicate that glucocorticoids stimulate the rate of MTV gene transcription in J2.17 but not in J2.15; in contrast, no labeled RNA hybridizing to flanking sequences was detected either in the uninfected or in the infected cells. We conclude that the host site of integration of MTV need not be transcriptionally active or hormonally responsive to permit viral gene expression. Furthermore, these rate measurements indicate that glucocorticoid-stimulated MTV RNA synthesis in J2.17 does not reflect readthrough transcription from a regulated cellular promoter. This notion is independently supported by transcript mapping experiments showing that the 5' terminus of nuclear MTV RNA is at a site on MTV DNA approx 1.2 kb downstream from the host-viral junction. Thus our data are consistent with the presence of a hormone-responsive element within the provirus. (Author abstract) (32 Refs)

19. HOST SUSCEPTIBILITY TO ENDOGENOUS VIRUSES: DEFECTIVE, GLYCOPROTEIN-EXPRESSING PROVIRUSES INTERFERE WITH INFECTIONS.

Robinson HL, Astrin SM, Senior AM, Salazar FH
Worcester Foundation for Experimental Biology, Shrewsbury, MA, 01545
J Virol; 40(3):745-751 1981

Three defective endogenous avian leukosis viruses, ev3, ev6 and ev9, interfered with subgroup E virus infections. ev3, ev6, and ev9 expressed high levels of subgroup E envelope glycoproteins. These glycoproteins reduced the activity of cellular receptors for subgroup E viruses. ev3 and ev6 protected chickens and cultured cells from subgroup E virus infections. (Author abstract) (40 Refs)

20. ASSOCIATION OF MURINE LEUKEMIA VIRUS GAG ANTIGEN WITH EXTRACELLULAR MATRICES IN PRODUCTIVELY INFECTED MOUSE CELLS.

Edwards SA, Lin YC, Fan H
(c/o Fan) Dept. Molecular Biology and Biochemistry, Univ. California, Irvine, CA, 92717
Virology; 116(1):306-317 1982

The gag gene of murine leukemia virus (MuLV) encodes a nonstructural glycosylated polyprotein which appears at the cell surface, in addition to the polyprotein precursor for the virion internal structural proteins. The surface localization of gag nonstructural protein is reported here. Immunofluorescent staining of unfixed monolayers of Moloney MuLV-infected NIH/3T3 cells using anti-p30 serum as the primary antibody revealed an unusual pattern of gag antigen at the attached cell surface: highly organized ca ble-like structures. Stained cable-like structures were also observed in regions lacking cells or cell processes, which suggested that extracellular gag antigen may be associated with extracellular matrices. This was supported by the fact that detergent treatment of cell monolayers in a manner designed to removed intact cells but preserve extracellular matrices did not affect the cable-like anti-p30 staining patterns. Immunofluorescent staining with anti-gp70 serum revealed a different pattern than the anti-p30 staining, which indicates that surface gag antigen and envelope glycoprotein are not physically associated at the cell surface. Similar staining patterns were observed in mouse cells productively infected with a different strain of MuLV (AKR), and in mink cells productively infected with a mink cell focus-inducing (MCF) derivative of Rauscher MuLV. (Author abstract) (30 Refs)

21. DETECTION BY RADIOIMMUNOASSAY OF ANTIGENS RELATED TO THE P30 POLYPEPTIDES OF PRIMATE TYPE C ONCOVIRUSES IN PERIPHERAL LEUKOCYTES FROM PATIENTS WITH CHRONIC MYELOGENOUS LEUKAEMIA.

Toth FD, Vaczi L, Kiss J, Rethy A, Kiss A, Rak K
Inst. Microbiology, Univ. Medical Sch., 4012 Debrecen, Hungary
Acta Virol (Praha); 25(6):376-380 1981

Leukocytes from patients with chronic myelogenous leukemia were examined for antigens related to the p30 polypeptides of baboon endogenous virus (BaEV) and gibbon ape leukemia virus (GaLV). Samples from patients with the quiescent phase of the disease proved to be negative or contained p30 of BaEV as the only viral antigen. In cases of blastoid crisis or acceleration, an antigen related to p30 of GaLV could be detected. In five of six patients, acceleration or blastoid crisis was preceded by expression of GaLV p30. (Author abstract) (15 Refs)

22. EXPRESSION OF BOVINE LEUKEMIA VIRUS GENOME IS BLOCKED BY A NONIMMUNOGLOBULIN PROTEIN IN PLASMA FROM INFECTED CATTLE.

Gupta P, Ferrer JF
Cooperative Leukemia Studies Unit, Sch. Veterinary Medicine, Univ. Pennsylvania, Kennett Square, PA, 19348
Science; 215(4531):405-407 1982

Plasma of cattle infected with bovine leukemia virus contains a soluble factor that blocks the expression of the viral genome in cultured lymphocytes. The blocking factor is not present in plasma of bovine leukemia virus-free cattle or of cattle infected with common bovine viruses. Blocking of bovine leukemia virus expression by the plasma factor is reversible, and seems to be mediated by a nonimmunoglobulin protein molecule. (Author abstract) (13 Refs)

23. EXPRESS-METHOD OF DETERMINATION OF SENSITIVITY OF CHICKENS TO ONCORNAVIRUSES.

Tulev IuV
Inst. Veterinary Medicine, Leningrad, USSR
Veterinariia; (11):28-30 1981

Modified method of determination of chickens' sensitivity to Rous sarcoma virus (RSV) was developed. The technique consisted of incubation of the trypsinized cells of the pulp of the feather with different doses of RSV, determination of the changes in the color of the medium, and estimation of the index of resistance. (no Refs) (In RUS)

24. ONCORNA VIRUSES IN N-METHYL-N-NITROSOUREA-INDUCED LYMPHOMAS IN MICE.

Pinter A, Borzsonyi M, Torok G, Surjan A, Csik M
Orszagos Kozegeszsegugyi Intezet, Budapest, Hungary
Magy Onkol; 25(4):227-235 1981

Fifteen newborn (C57BL/6xDBA/a) F1 (BDF1) hybrid mice were treated with N-methyl-N-nitrosourea (MNU: 20 mg/kg ip). Five of the 15 animals developed thymic lymphomas, identified histologically and immunologically as lymphoblastic lymphomas, during the 145-day observation period, but no tumors were found in the 20 control animals treated with physiological saline soln only. Unlike the thymic cells of the young control animals, the tumor cells produced oncorna viruses growing in murine tissues only. According to their protein expression, the endogenous, N-tropic viruses represent a homogeneous population. Similar virus was found in thymic cells of a 5-mo-old mouse, which suggests the possibility of age-dependent, spontaneous activation. Since spontaneous lymphoma does not occur in BDF1 mice under the age of 1.5 yr, the viruses isolated are probably not oncogenic, but possess a tumor-promoting property. (19 Refs) (In HUN)

GENETICS

25. ROUS SARCOMA VIRUS MUTANT LA3382 IS DEFECTIVE IN VIRION GLYCOPROTEIN ASSEMBLY.

Hardwick JM, Hunter E
Dept. Microbiology, Univ. Alabama Birmingham, Birmingham, AL, 35294
J Virol; 40(3):752-761 1981

LA3382 is a temperature-sensitive replication-defective mutant of Rous sarcoma virus that contains four active mutations. In this study we performed experiments to determine the biochemical defect that blocks the synthesis of infectious virus late in the replication cycle. At the nonpermissive temperature (41 C) cells infected with LA3382 synthesized virus particles which were noninfectious and exhibited significant reductions in the amounts of gp85 and gp37 present in the virions. An analysis of the intracellular viral polypeptides indicated the the precursor of the viral glycoproteins (Pr95) was synthesized normally but underwent cleavage at a reduced rate at the restrictive temperature. Pr95 did not accumulate in infected cells and was inserted into mutant virions at 41 C; however, Pr95 was cleaved in such a way that gp85 was released from the viruses and could be detected in the supernatant medium by immunoprecipitation. The virus-free glycoprotein was indistinguishable from wild-type gp85 and may have been released due to an anomalous cleavage. Pulse-chase experiments also indicated that the Pr180 polyprotein precursor of the reverse transcriptase was cleaved to the active form of the enzyme more slowly at 41 C in LA3382-infected cells. This accounted for the twofold lower level of polymerase activity found in mutant virions at 41 C, a defect which probably did not account for the observed 20-to 50-fold reduction in infectivity. Furthermore, the replication defect was not complemented by an env deletion mutant Rous sarcoma virus [RSV(-)], which should complement a pol defect. Therefore, we concluded that the major lesion that impairs replication in LA3382 is within the env gene. (Author abstract) (25 Refs)

26. LOCATION OF THE GENE RESPONSIBLE FOR ROUS SARCOMA REGRESSION IN THE B-F REGION OF THE B COMPLEX (MHC) OF THE CHICKEN.

Plachy J, Benda V
Inst. Molecular Genetics, Czechoslovak Acad. Sciences, 160 00 Praha, Czechoslovakia
Folia Biol (Praha); 27(5):363-368 1981

The fate of tumors induced by two strains of avian sarcoma virus (Prague strain of Rous sarcoma virus subgroups C and B77-C) was studied in the inbred chicken lines CB, CC, and CB/R1. Chickens received a dose of virus equivalent to 100 focus-forming units sc in the left wing web. Starting 10 days after inoculation, tumor growth and regression were assessed during a 10-wk period. Birds were considered regressors when the tumor had regressed completely. After infection with either of the two viruses, Rous sarcomas regressed in the CB and CB/R1 lines (identical in the B-F region of the B complex). Progressive tumor growth occurred in the CC line, which differed from the CB and CB/R1 in the B-F region but was identical in the B-G region to the CB/R1 line. The gene responsible for Rous sarcoma regression is apparently located in the B-F region of the B complex. (23 Refs)

27. GENETIC CONTROL OF ROUS SARCOMA REGRESSION IN INBRED LINES OF CHICKENS.

Plachy J, Albrecht V
Inst. Molecular Genetics, Czechoslovak Acad. Sciences, 160 00 Praha, Czechoslovakia
Folia Biol (Praha); 27(5):289-300 1981

The fate of tumors induced by the Prague strain of Rous sarcoma virus (RSV) subgroup C was studied in highly inbred chicken lines. The lines CB and CC, and WA and WB, congeneic at the B complex, the major histocompatibility complex of the chicken, were used. The CB and CC lines differ only in the B haplotype, as do the WA and WB lines. Included in the study were (CB x CC)F1 hybrids and backcross progeny of the CB and CC lines. All birds were blood typed before use. Birds received 10(3), 10(2), or 10(1) focus-forming units/animal sc in the left wing web. The pattern of tumor regression or progression was assessed weekly beginning 7 days post-inoculation for a 10 wk period, in birds 4-8 wk, 12-16 wk, or 1 yr old at the time of inoculation. Results demonstrated that Rous sarcoma regression in the congeneic CB and CC lines is controlled by a gene within the B region of the chromosome. Another congeneic pair in the WA and WB lines also differed in ability to regress RSV-induced tumors and a gene within the B complex also appeared to have a significant role in the regression of Rous sarcoma. (24 Refs)

IMMUNOLOGICAL STUDIES

28. HELPER VIRUSES ASSOCIATED WITH AVIAN ACUTE LEUKEMIA VIRUSES INHIBIT THE CELLULAR IMMUNE RESPONSE.

Rup BJ, Hoelzer JD, Bose HR
(c/o Bose) Dept. Microbiology, Univ. Texas, Austin, TX, 78712
Virology; 116(1):61-71 1982

The cellular immune competence of lymphocytes obtained from birds infected with acute or chronic leukemia viruses was studied. The in vitro blastogenic response of thymus-derived lymphocytes (T cells) to the mitogens phytohemagglutinin

(PHA) and concanavalin A (Con A) correlates with the ability of birds to elicit a cellular immune response. The PHA response of splenic lymphocytes from birds infected with the avian acute leukemia viruses, myelocytomatosis virus strain 29 (MC29), avian erythroblastosis virus (AEV), avian myeloblastosis virus (AMV), or reticuloendotheliosis virus (REV-T), was completely suppressed within 1 wk after virus infection. The early induction of immunosuppression is therefore a general feature of infection of chickens by avian acute leukemia viruses. Spleen cells from chickens infected with the chronic leukemia viruses, Rous-associated viruses (RAVs) Types 1 and 3, exhibited PHA responses similar to those of uninfected birds. In contrast, lymphocytes from RAV-2 infected birds had suppressed PHA responses. Acute leukemia viruses are replication-defective and are associated with replication-competent nontransforming helper viruses. When chickens were infected with helper viruses isolated from the acute leukemia virus stocks by endpoint dilution, the T-cell response to various T-cell mitogens was completely suppressed. the helper viruses, therefore, contribute to the immunosuppression which occurs during the development of avian acute leukemia. The rapid lethality of the acute leukemia virus could be, in part, the result of the immunosuppressive activity of the associated helper viruses. Though all the acute leukemia viruses severely immunosuppress their hosts, the mechanism by which the immunosuppression was induced by these viruses differed. REV-T was the only acute leukemia virus which induced a population of splenic suppressor cells. All the viruses of the leukosis-sarcoma complex tested which had subgroup B specificity were immunosuppressive while those of subgroup A were not. These results suggest that immunosuppression by these viruses may be related to subgroup specificity. (Author abstract) (49 Refs)

29. SYNTHESIS OF A VIRAL PROTEIN WITH MOLECULAR WEIGHT OF 30,000 (P30) BY LEUKEMIC CELLS AND ANTIBODIES CROSS-REACTING WITH SIMIAN SARCOMA VIRUS P30 IN SERUM OF A CHRONIC MYELOID LEUKEMIA PATIENT.

Derks JP, Hofmans L, Bruning HW, Rood JJ
Dept. Immunohematology, Bloodbank, Univ. Hosp., Building 23, Rijnsburgerweg 10, 2333 AA Leiden, The Netherlands
Cancer Res; 42(2):681-686 1982

We studied a patient with a Philadelphia chromosome-positive chronic myeloid leukemia, who died in relapse after multiple transfusions and grafting with bone marrow from his monozygotic twin brother (referred to as 'donor' in this paper). We present data indicating that this patient may have had a retrovirus infection and that this virus is related to the group of exogenous primate Type C retroviruses. Antibodies to simian sarcoma virus (SSV) mol wt 30,000 protein (p30) but not endogenous feline virus RD-114 could be found in patient but not donor serum. Patient but not donor cells were able to actively synthesize a p30 protein that could be precipitated with patient serum and rabbit anti-SSV p30 but not with donor serum or rabbit anti-RD-114 p30. Patient p30 resembles SSV p30 but not RD-114 p30 in peptide mapping by limited proteolysis and subsequent slab gel electrophoresis. Patient but not donor cells were able to actively synthesize a mol wt 78,000 protein that could be precipitated with goat anti-SSV. An enzyme with properties of reverse transcriptase was increased 30-fold in patient cells when compared with donor and other control cells. Related to the presence of widespread infectious agents may be the finding that, in the course of the patient's disease, donor serum showed increasing amounts of possibly immunoregulatory antibodies, reactive with autologous and, more effectively, with patient-derived cell membrane mol wt 80,000 protein (a possible idiotypic receptor structure) and mol wt 94,000 protein (a T-cell alloantigen). (Author abstract) (31 Refs)

30. QUANTITATIVE VARIATIONS IN THE EXPRESSION OF H-2 ANTIGENS ON MURINE LEUKEMIA VIRUS-INDUCED TUMOR CELLS CAN AFFECT THE H-2-RESTRICTION PATTERNS OF TUMOR-SPECIFIC CYTOLYTIC T LYMPHOCYTES.

Plata F, Tilkin AF, Levy JP, Lilly F
Unite d'Immuno-Parasitologie, Institut Pasteur, 25 rue du Docteur Roux, 75015 Paris, France
J Exp Med; 154(6):1795-1810 1981

Expression of major histocompatibility antigens (H-2) Kd and Dd was quantified in three different leukemia cell lines induced by Gross murine leukemia virus (MuLV) in BALB/c (H-2d) mice. Preferential recognition of Gross MuLV-induced tumor antigen with H-2Kk or H-2Dd antigen by tumor-specific cytotoxic T lymphocytes (CTL) from BALB/c mice was correlated with the quantitations. The three BALB/c tumor lines differed in amount of H-2Kd and H-2Dd antigens expressed on the cell surface; the variations were reflected in quality as target cells to Gross MuLV-specific CTL from BALB/c mice. The results indicated that restriction of tumor-specific CTL activity by H-2 can be directed at the target cell level by the quantitative modulation of H-2K or H-2D antigen expression; separate tumors induced by the same MuLV in the same or in H -2-congeneic strains of mice may vary in absolute amount of H-2K or H-2D antigen expressed on the cell surface. (35 Refs)

31. ANTIBODIES AGAINST FELINE AND GIBBON APE REVERSE TRANSCRIPTASE ON SURFACE OF SPLEEN CELLS IN HUMAN MYELOGENOUS LEUKEMIA.

Jacquemin PC
Brussels Branch, Ludwig Inst. Cancer Res., 74 avenue Hippocrate, UCL 74.59, B-1200 Bruxelles, Belgique
Eur J Cancer Clin Oncol; 17(12):1283-1286 1981

We reported that antibody bound to blood leukocytes of patients in chronic myelogenous leukemia neutralize reverse transcriptase. The specificity of neutralization depended on the phase of the disease. Antibody bound to chronic phase leukemia cells neutralized Gibbon Ape leukemia virus reverse transcriptase, while that bound to blastic phase cells neutralized Feline leukemia virus reverse transcriptase. Spleen cells obtained from patients with chronic myelogenous leukemia have surface-bound immunoglobulins that recognize both reverse transcriptases. These data in the spleen suggest the existence of a progressive shift in cell population from a chronic phase type cell to a blastic phase type cell. (Author abstract) (9 Refs)

32. DIFFERENTIAL REGULATION OF H-2 ANTIGEN EXPRESSION IN TUMORS AND ITS BIOLOGIC CONSEQUENCES.

Schmidt W, Alonso A, Leben L, Festenstein H, Martin WJ, Meruelo D, Schirrmacher V, Rajan, Lennox ES, Bach FH, Rogers MJ
Dept. Virology FB23, Justus-Liebig-Univ., D-6300 Giessen, W. Germany
Transplant Proc; 13(4):1814-1818 1981

Variations in H-2 antigen expression and their effects on immune response in 10 mouse leukemia cell lines were studied. Cell lines were derived from spontaneous leukemias in AKR mice and AKR/Gross murine leukemia virus (MuLV)-induced leukemias in BALB.K(H-2k) mice, and were designated

K36.16, k-GV, 110, 344, 389, 424, 339, 365, 369, and 422. Assays of complement-dependent cytotoxicity indicated that expression of both H-2Kk and H-2dk antigens was slightly increased in 365 and highly increased in 339 and 369. Expression of H-2.Kk antigen was reduced and expression of H-2Dk was normal in 110 and 424. Expression of H-2Kk was absent, and expression of H-2Dk was normal or reduced in K36.16, k-GV, 334, 389, and 422. Loss of H-2Kk, when observed, was consistent within cell lines in vivo and in vitro. Results of cytotoxicity assays were confirmed by similar results with absorption and immunofluorescence assays. Labeling experiments with [3H]- or [14C]-arginine indicated that differences in H-2Kk and H-2Dk expression are reflected at the level of biosynthesis and are not due to turnover or blocking at the cell surface. Results of stimulation of cytotoxic effector cells (CTL) with k-GV or 369 tumor cells showed that cytolysis of cells lacking H-2Kk is low; H-2Kk is apparently important for H-2-restricted cytolysis of cells by CTL sensitized against viral antigens. Changes in H-2Kk expression may play an important role in the development of leukemia. (12 Refs)

33. A SIGNIFICANT ROLE OF PROXIMITY OF HVJ-ANTIGEN IN THE GENERATION OF TUMOR IMMUNITY.

Kawashima K, Watanabe E, Kato Y, Suzuki H, Minami S, Isobe K, Ogura M, Nagura E, Yamada K
First Dept. Internal Medicine, Nagoya Univ. Sch. Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466, Japan
Gan; 72(6):955-958 1981

According to the blocking test for proximity of cell surface antigens, L1210 leukemia-associated antigen was not linked to molecules carrying H-2d antigen or murine leukemia virus-associated antigen, but there was a close association between HVJ-associated antigen and L1210 leukemia-associated antigen on the surface membrane of HVJ-pi-infected L1210 leukemia cells. Once L1210 leukemia cells were infected with HVJ-pi, their adsorptive power was found to be greater than that of uninfected cells by quantitative absorption analysis. These phenomena may lead to a better recognition by the host of L1210 leukemia-associated antigen, followed by generation of tumor immunity. (Author abstract) (13 Refs)

34. INCREASED RESPONSES TO LYMPHOKINES ARE CORRELATED WITH PRELEUKEMIA IN MICE INOCULATED WITH MOLONEY LEUKEMIA VIRUS.

Lee JC, Ihle JN
Biological Carcinogenesis Program, NCI-Frederick Cancer Res. Facility, Frederick, MD, 21701
Proc Natl Acad Sci USA; 78(12):7712-7716 1981

In various mouse strains, inoculation with Moloney leukemia virus results in the establishment of an acute viremia which in most cases is followed by the induction of leukemia. Also associated with the viremia is the development of a chronic cellular immune response detectable in vitro by the ability of viral proteins to induce splenic lymphocyte proliferation. Previous studies have demonstrated that, in the absence of this cellular immune response, leukemia does not develop irrespective of whether viremia is present. In vitro proliferative responses to antigens involve the nonspecific response of various subpopulations of lymphocytes to lymphokines produced by antigen-specific Thy 1+, Lyt 1+,2-lymphocytes. The studies presented here concern the effects of a chronic immune response in viremic mice on the frequency of lymphocytes capable of responding to lymphokines in vitro. The data demonstrate that the number of responsive lymphocytes is increased 30-to 100-fold in preleukemic mice and that such increases are dependent upon the induction of an immune response in viremic mice. The role of this altered immune response in leukemia is discussed. (Author abstract) (18 Refs)

35. COMPARATIVE EFFECTS OF AZATHIOPRINE CYCLOPHOSPHAMIDE AND FRENTIZOLE ON CELLULAR IMMUNITY IN MICE.

Smith SR, Terminelli C, Kipilman CT, Smith Y
Dept. Allergy and Inflammation, Schering Corporation, 60 Orange St., Bloomfield, NJ, 07003
J Immunopharmacol; 3(2):133-170 1981

The immunosuppressive properties of cyclophosphamide (CPA), azathioprine (AP), and frentizole (FZ) were compared. Systemic graft vs host reaction (GVHR; splenomegaly assay) was completely suppressed in mice treated with AP (25 mg/kg) or CPA (5 mg/kg); FZ gave some suppression. When spleen cells from immunosuppressant-treated animals were injected into F1 hybrids systemic GVHR was inhibited by CPA (10 and 20 mg/kg), by AP (25 mg/kg), but not by FZ. AP and FZ (po) did not suppress local GVHR induced by injection of spleen cells into the left hind foot, but 5 mg/kg CPA (po) gave 70% suppression. The proliferative ability of spleen cells in irradiated A/J B6A hybrids was markedly suppressed in mice treated po or by ip injection with CPA or AP, but FZ had no effect. Only CPA prevented oxazolone-induced increase in lymph node wt in a dose-responsive way; FZ and AP had some weak effects. Spleen cells from mice treated with the three drugs showed varying responses when cultured with concanavalin A, phytohemagglutinin, or lipopolysaccharide. Spleen cells from C57BL/6 mice treated po with AP or CPA responded slightly to irradiated DBA/2J spleen cells, whereas cells from FZ-treated mice responsed normally. Murine sarcoma virus-induced tumors responded by some mass reduction in animals treated with AP and CPA po for 12 days after tumor induction. A single dose of 300 mg/kg of FZ or CPA actually enhanced tumor growth when administered 24 hr before virus inoculation. Oral treatment (21 days) with 25-50 mg/kg AP or 20 mg/kg CPA retarded SaI-spindle cell fibrosarcoma, but FZ had no effect. CPA, FZ, and AP can induce significant changes in some lymphoid tissues. CPA seems to be the most effective of the three drugs in suppressing cellular immune responses of mice. (32 Refs)

36. TUMOR SPONGE IMPLANTATION: AN IN VIVO METHOD FOR STUDYING SYNGENEIC, PRIMARY ANTITUMOR LYMPHOCYTE RESPONSES.

Vallera DA, Mentzer SJ, Maizel SE
Dept. Lab. Medicine and Pathology, Univ. Minnesota, Box 367, Mayo Memorial Building, Minneapolis, MN, 55455
Cancer Res; 42(2):397-404 1982

Sponge matrices surgically implanted in the sc spaces of the backs of normal BALB/c mice were injected with a 'regressor' dose of Moloney virus-induced BALB/c tumor cells. The kinetics of the generation of cytotoxic cells within the sponge was studied over a 22-day period in a short-term 51Cr release assay. Cytotoxic activity peaked on Day 16 and then declined to negligible levels by Day 22. When the cellular composition of implanted tumor sponges was examined on Day 16, it was found to be 30 to 40% myeloperoxidase-positive cells, 15 to 25% surface Ig-positive cells, and 40 to 50% theta-positive cells. Treatment with anti-Thy 1.2 plus complement eliminated the cytotoxic response on Day 16. The ratio of T-cells to tumor cells within the sponge was determined by immunofluorescence. Kinetic studies showed that the number of theta-positive cells increased well before cytolytic activity was detected, possibly reflecting increasing numbers of amplifier T-cells or cytotoxic cell precursors. A later decline in theta-positive cells correlated directly with decreased cytotoxicity. Furthermore, onset of cytotoxic activity also correlated with a decline in the percentage of Moloney murine sarcoma virus tumor cells within the sponge. Sponge cells isolated on Day 16 (peak cytotoxicity), mixed with lethal dosages of Moloney murine sarcoma virus tumor cells, successfully neutralized the lethal challenge demonstrating the in vivo antitumor efficacy of these effector cells. Sponges were also implanted in mice which had been immunized with a single injection of Moloney murine sarcoma virus cells. Inoculation of the sponge with tumor cells resulted in a second set response in which cytotoxic cells appeared much earlier than in unsensitized animals. Cells from spleen, lymph node, or peritoneal cavity of normal or presensitized animals with tumor sponge implants were not cytotoxic, suggesting a highly localized response. (33 Refs)

37. SPECIFICITY OF SYNGENEIC MONOCLONAL ANTIBODIES AGAINST CELL SURFACE ANTIGENS ON CHEMICALLY INDUCED MOUSE FIBROSARCOMAS.

Klein PA

Tumor Biology Unit, Dept. Pathology, Coll. Medicine, Univ. Florida, Gainesville, FL, 32610

Transplant Proc; 13(4):1762-1764 1981

Development and characterization of 16 monoclonal antibodies (McAb) against tumor-specific transplantation antigens (TSTA) are reported. McAb were developed by immunizing C57BL/6 and BALB/c mice with their own syngeneic, chemically induced fibrosarcomas bearing unique TSTA; the formation of hybridomas followed. Radioimmunoassays were carried out with a large panel of normal cells, tumor cells, and ecotropic and xenotropic murine leukemia viruses (MuLV). Competitive binding assays used tumor cells and MuLV against well-characterized anti-MuLV gp70 and p15(E) McAb. No highly restrictive tumor specificity was found for any of 16 McAb tested. All McAb showed either MuLV-dependent or MuLV-independent cross-reactivity with several mouse tumor strains. Results obtained with five McAb are tabulated. Reactions to anti-MuLV indicated that M3, PC11, and CS-1 tumor strains express gp70 and p15(E) antigens of ecotropic and/or xenotropic viruses on the cell surface. McAB L1 and 4B1 were specific for tumors bearing MuLV antigens. The 4B1 McAb was specific for a molecule similar or identical to the gp70a epitope of ecotropic MuLV. Three McAb showed tumor reactions independent of MuLV antigens. Failure to produce a tumor-specific McAb may be due to differences in T and B cell function or to sampling luck. (9 Refs)

38. IMMUNOTOXICITY OF PENTACHLOROPHENOL (PCP): INCREASED SUSCEPTIBILITY TO TUMOR GROWTH IN ADULT MICE FED TECHNICAL PCP-CONTAMINATED DIETS.

Kerkvliet NI, Baecher-Steppan L, Schmitz JA
Sch. Veterinary Medicine, Oregon State Univ., Corvallis, OR, 97331
Toxicol Appl Pharmacol; 62(1):55-64 1982

Immune competence in mice following chronic dietary exposure to pentachlorophenol (PCP), and the effects of PCP exposure on susceptibility to virus infection and tumor growth, cytotoxic T-cell response, and macrophage phagocytic function in in vitro assays were examined. Adult male C57Bl/6 mice were fed diets containing 50 or 500 ppm pure (99+%) or technical grade (86%) PCP for 10-12 wk prior to assessment of immunocompetence. Exposure of mice to technical grade PCP resulted in enhancement of tumor susceptibility. The incidence of progressive methylcholanthrene (MCA)-induced transplanted tumors increased from 35% in controls to 67% in animals exposed to 50 ppm technical PCP and 82% in animals exposed to 500 ppm technical PCP. Mortality following primary Moloney sarcoma virus (MSV) inoculation and secondary MSV-transformed sarcoma cell (MSB) challenge increased from 19% in controls to 45% in animals exposed to 50 ppm technical PCP and 73% in animals exposed to 500 ppm technical PCP. An additional 50% of the MSV/MSB challenged mice exposed to 50 ppm technical PCP exhibited tumor dissemination into the spleen. Animals exposed to pure PCP did not exhibit enhancement of primary MCA- or MSV-induced tumor growth. Splenic tumor development was observed in 22% of the MSV/MSB challenged mice exposed to 50 ppm pure PCP, and in 44% of the MSV/MSB challenged mice exposed to 500 ppm PCP. Control mice did not develop splenic tumors. Significant depression in T-cell cytolytic activity and enhancement of macrophage phagocytosis in animals exposed to technical PCP were noted. No significant changes in in vitro immune response were noted with cells from pure PCP-exposed animals. (26 Refs)

OTHER RELATED STUDIES

39. VIRUSES SIMILAR TO HEPATITIS B VIRUS (ICRONS).

Blumberg BS
Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA, 19111
Hum Pathol; 12(12):1107-1113 1981

In 1971, on the basis of the unusual clinical and epidemiologic characteristics of hepatitis B virus, we postulated the existence of a class of viruses that we termed icrons. An increased understanding of the molecular biology of hepatitis B virus resulted in the discovery, by Summers and his colleagues, of the woodchuck hepatitis virus. This virus is common in the North American woodchuck (Marmota monax) and is associated with primary cancer of the liver in this animal. Subsequently similar viruses were found in Beechey ground squirrels in California by Marion and her coworkers and domesticated (Pekin) ducks from the United States by Mason and his coworkers. In the latter the virus infects the liver and presumably is associated with disease of this organ. The discovery of additional viruses similar to hepatitis B virus in animals other than man and their association with cancer of the liver encourages the continuing search for other virus-cancer associations for which prevention methods might be effective. (Author abstract) (20 Refs)

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RNA VIRUSES ASSOCIATED WITH CANCER

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JULY, 1982

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VIRUS ISOLATION AND CHARACTERIZATION

1. NATURAL ANTIBODIES TO HUMAN RETROVIRUS HTLV IN A CLUSTER OF JAPANESE PATIENTS WITH ADULT T CELL LEUKEMIA.

Robert-Guroff M, Nakao Y, Notake K, Ito Y, Sliski A, Gallo RC
Dept. Cell Biology, Litton Bionetics, Inc., Kensington, MD, 20895
Science; 215(4535):975-978 1982

Human T cell lymphoma leukemia virus (HTLV) is a human retrovirus (RNA tumor virus) that was originally isolated from a few patients with leukemias or lymphomas involving mature T lymphocytes. Here we report that the serum of Japanese patients with adult T cell leukemia, but not the serum of tested normal donors, contains high titers of antibodies to HTLV. These observations, together with data from Japan showing that adult T cell leukemia is endemic in southwest Japan, suggest that HTLV is involved in a subtype of human T cell malignancy, including Japanese adult T cell leukemia. (Author abstract) (22 Refs)

2. ORIGIN AND BIOLOGICAL PROPERTIES OF A NEW FELINE SARCOMA VIRUS.

Rasheed S, Barbacid M, Aaronson S, Gardner MB

Dept. Pathology, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033

Virology; 117(1):238-244 1982

A new strain of feline sarcoma virus (GR-FeSV) was isolated from a spontaneous sarcoma of an 8-yr-old domestic house cat. The virus induced sarcomas at high incidence after a short latent period in fetal and newborn kittens and transformed cat embryo fibroblasts in vitro after 5 days. Compared to Gardner-Arnstein and the Snyder-Theilen strains of FeSV, GR-FeSV induced more pleomorphic sarcomas and larger, more rounded and discrete foci of cell transformation. GR-FeSV was shown to be defective for replication, and nonproducer transformed clones from several species were obtained at limiting GR-FeSV dilution. The defective sarcoma virus could be rescued from such transformants by superinfection with replication competent type-C viruses. The primary translational product of the GR-FeSV genome is a 70,000-dalton polyprotein that contains the amino-terminal domain of the FeLV gag gene precursor protein and a sarcoma virus-specific polypeptide. These results differentiate GR-FeSV from previously isolated FeSV strains, and establish it as an independent spontaneously occurring sarcoma virus isolate of the domestic cat. (Author abstract) (16 Refs)

3. HUMAN CANCERS AND HUMAN VIRUSES.

Waterson AP

Royal Postgraduate Medical Sch., London W12 0HS, England

Br Med J; 284(6314):446-448 1982

The connection between human cancers and human viruses is reviewed. Evidence of malignancies attributable to DNA viruses, similar to those of animals, is growing. A type of human leukemia retrovirus, the human T-cell leukemia virus, has been isolated. Hepatitis B virus has been shown to be of primary hepatocellular carcinoma and Epstein-Barr virus the cause of Burkitt's lymphoma and nasopharyngeal carcinoma; cytomegalovirus may be implicated in Kaposi's sarcoma and human papillomaviruses may cause skin cancer. To be implicated in oncogenesis, a virus should be found in tumor cells and be capable of transforming normal cells of the same species in vitro and inducing tumors in studies with animals. Human T-cell leukemia virus has been shown to be infectious when cultivated with human umbilical cord leukocytes, transforming them into virus-producing lines. Epstein-Barr virus causes disease only rarely on primary infection in childhood, but in adolescence or adult life it gives rise to infectious mononucleosis. Hepatitis caused by hepatitis B virus can be followed by chronic active hepatitis and cirrhosis and is a suspected cause of primary hepatocellular carcinoma. Malignant change has been reported in laryngeal papillomas, in genital warts, and in epidermodysplasia verruciformis. Factors other than viruses which influence malignant transformation are the genetic constitution and immune state of the patient. The virus-cell relation is not simple. (29 Refs)

VIRUS ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

4. TRANSFORMING GROWTH FACTOR(S) PRODUCTION ENABLES CELLS TO GROW IN THE ABSENCE OF SERUM: AN AUTOCRINE SYSTEM.

Kaplan PL, Anderson M, Ozanne B

Dept. Microbiology, Univ. Texas Health Science Center, 5323 Harry Hines Blvd., Dallas, TX, 75235

Proc Natl Acad Sci USA; 79(2):485-489 1982

Kirsten murine sarcoma virus (KiMSV)-transformed rat-1, normal rat kidney (NRK), and BALB/c 3T3 cells are capable of continual growth in a serum-free medium supplemented with transferrin and insulin but with no exogenous mitogenic growth factors. Cells transformed by a mutant of KiMSV that is temperature sensitive for the maintenance of transformation grow in this medium at the permissive temperature only. At the nonpermissive temperature, growth is dependent upon the presence of serum-free conditioned medium from the transformed cells. Normal rat-1 cells are also dependent upon factors from the transformed cells for growth in this serum-free/mitogen-free medium. The serum-derived growth factors, epidermal growth factor, and fibroblast growth factor have no effect on the transformed cells, although epidermal growth factor can replace transforming growth factors produced by KiMSV-transformed cells for the growth of rat-1 cells. Growth of the transformed cells in serum-free medium at clonal densities is dependent upon the presence of conditioned medium collected from the same cells grown to high densities. These results show that (i) growth in serum-free/mitogen-free medium is a general property of KiMSV-transformed cells and (ii) growth of the transformed cells in this medium is dependent upon the presence of growth factors known to be produced by the cells, and they provide support for the hypothesis that serum-free growth of KiMSV-transformed cells is dependent upon ectopically produced growth factors. (Author abstract) (19 Refs)

5. ISOLATION FROM MURINE SARCOMA CELLS OF NOVEL TRANSFORMING GROWTH FACTORS POTENTIATED BY EGF.

Roberts AB, Anzano MA, Lamb LC, Smith JM, Frolik CA, Marquardt H, Todaro GJ, Sporn MB

Lab. Chemoprevention, NCI, NIH, Bethesda, MD, 20205

Nature; 295(5848):417-419 1982

Two distinct classes of intracellular transforming growth factors (TGF) were isolated from Moloney sarcoma virus (MSV)-transformed 3T3 cells. One TGF competed with epidermal growth factor (EGF) for receptor binding sites, whereas the other did not. After high-performance liquid chromatography p urification, the colony-forming activity of the TGF that do not compete with EGF for receptor binding was enhanced 100-fold by the addition of EGF. The abiliity to enhance growth-stimulating effects of TGF was specific for EGF, as insulin, the insulin-like growth factors, platelet-derived growth factor, and nerve growth factor did not show this property. In contrast, the colony-forming activity of TGF that compete with EGF for receptor binding was not potentiated by EGF. The role of the new TGF in malignant transformation, wound repair, and embryogenesis are discussed. (24 Refs)

6. IN VITRO STUDIES OF THE MECHANISM OF LEUKEMOGENESIS. II. CHARACTERIZATION OF ENDOGENOUS MURINE LEUKEMIA VIRUSES ISOLATED FROM AKR THYMIC EPITHELIAL RETICULUM CELL LINES.

Yanagihara K, Hamada K, Seyama T, Imamura N, Yokoro K
Dept. Pathology, Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Hiroshima, Japan
J Virol; 41(2):360-366 1982

Thymic epithelial reticulum (TER) cell lines were established from thymuses of a young healthy AKR mouse (A2T), a preleukemic AKR mouse (A6T), and two lymphoma-bearing AKR/Ms mice (ASLT-1 and ASLT-2). Numerous Type-C virus particles with occasional budding forms were observed in all cell lines. Expression of XC-detectable, N-tropic, ecotropic virus was observed in every cell line, whereas the presence of xenotropic and mink cell focus-inducing (MCF) viruses could be detected only in TER cells derived from preleukemic and leukemic mice. Expression of xenotropic virus in various cells of newborn and young AKR mice could readily be induced by IUdR treatment, whereas MCF virus was never detected in these cells, with the exception of the A2T cell line after more than 20 passages, in which MCF virus with dual-tropic infectivity emerged in addition to ecotropic and xenotropic viruses. These spontaneous and induced MCF viruses were purified, and their virological properties were characterized. The cloned MCF viruses (MCFs AT1, AT2, AT3, and AT4-IU) showed dual tropism and produced cytopathic effect-like foci in mink lung cells. Preinfection with either ecotropic or xenotropic virus interfered with the infectivity of MCF viruses. Spontaneous leukemogenesis in AKR mice was accelerated by the inoculation of MCF viruses. These findings indicate that TER cells could serve as the host cells for the genetic recombination of the endogenous MuLV; the recombinant MuLV, MCF virus, appears to be most closely associated with leukemogenesis in AKR mice. (Author abstract) (29 Refs)

7. TYROSINE PHOSPHORYLATION OF A 50K CELLULAR POLYPEPTIDE ASSOCIATED WITH THE ROUS SARCOMA VIRUS TRANSFORMING PROTEIN PP60SRC.

Gilmore TD, Radke K, Martin GS
(c/o Martin) Dept. Zoology, Univ. California, Berkeley, CA, 94720
Mol Cell Biol; 2(2):199-206 1982

A 50,000 dalton cellular polypeptide (50K-CP) associated with the transforming protein pp60src of the Rous sarcoma virus (RSV) was studied. 50K-CP from cells that were uninfected or infected with a transformation-defective RSV contained phosphoserine but little or no phosphotyrosine (PT). 50K-CP from cells infected by transforming RSV showed a 50-fold increase in PT, indicating that pp60src is required for phosphorylation of 50K-CP at tyrosine. 50K-CP may be a high-affinity substrate of pp60src. (31 Refs)

8. CYTOSOLIC MALIC DEHYDROGENASE ACTIVITY IS ASSOCIATED WITH A PUTATIVE SUBSTRATE FOR THE TRANSFORMING GENE PRODUCT OF ROUS SARCOMA VIRUS.

Rubsamen H, Saltenberger K, Friis RR, Eigenbrodt E
Paul-Ehrlich-Institut, Paul-Ehrlich-Strasse 42-44, Frankfurt am Main, W. Germany
Proc Natl Acad Sci USA; 79(2):228-232 1982

A cellular protein of apparent Mr 34,000-36,000 was suggested as a possible physiological substrate for the protein kinase (EC 2.7.1.37) activity associated with the transforming gene product of Rous sarcoma virus. We find this protein to migrate with an apparent Mr of 38,000 in NaDodSO4/polyacrylamide gels. It was not separable from cytosolic malic dehydrogenase activity when purified by chromatography on DEAE-Sephacel, hydroxylapatite, poly(A)-Sepharose, and blue Sepharose, by gel filtration, and by isoelectric focusing. The Mr 38,000 protein as well as cytosolic malic dehydrogenase activity focused with a pI of 7.5. In gel filtration experiments, both displayed an apparent native Mr of 68,000. The malic dehydrogenase activity contained in homogeneous preparations of the Mr 38,000 protein had a specific activity of up to 130 units/mg of protein. The recovery of the enzyme was 5-10% of the activity in the extract. Antiserum against the Mr 38,000 protein inactivated the malic dehydrogenase activity associated with the Mr 38,000 protein. (Author abstract) (43 Refs)

9. NEURAMINIDASE ACTIVITY AND CELL SURFACE SIALIC ACID TURNOVER IN ROUS SARCOMA VIRUS TRANSFORMED CHICK EMBRYO FIBROBLASTS.

Myers-Robfogel MW, Spataro AC, Bosmann HB, Morgan HR
Dept. Pharmacology and Toxicology, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY, 14642
Cancer Biochem Biophys; 5(3):141-146 1981

Activities of neuraminidase (Ndase), cytidine monophosphate-N-acetyl neuraminic acid synthetase (CMP-AcNeu synthetase), and cytidine monophosphate-N-acetylneuraminic acid hydrolase (CMP-AcNeu hydrolase) were determined in primary cultures of chick embryo fibroblasts (CEF) transformed with the Schmidt-Ruppin strain of Rous sarcoma virus (RSV) and CEF infected with a Rous-associated virus that did not transform them. Total acid-labile sialic acid (SA) was decreased in RSV-CEF cells, but not in RAV-CEF cells. Ndase-accessible SA was increased above the control levels in both transformed and untransformed infected cells. Total Ndase activity in whole cell homogenates assay by neuraminlactitol-(3H) was elevated at both pH 4.3 and pH 6.8 in RSV-CEF but not in RAV-CEF, and cell-surface Ndase activity was also elevated in RSV-CEF according to release of (14C)-SA from cells preincubated with CMP-(14C)N-acetylneuraminic acid. Transformed and untransformed cells did not differ from controls in activities of CMP-AcNeu synthetase and CMP-AcNeu hydrolase. Ndase activity in the cell and at the cell surface appears important in maintaining the altered SA-containing macromolecules of the transformed cell surface. (16 Refs)

10. STUDIES ON THE ACTIVITY OF ALPHA-FETOPROTEIN GENE.

Choi NH, Higashi T
Dept. Biochemistry, Sch. Pharmaceutical Sciences, Showa Univ., 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142, Japan
Chem Pharm Bull (Tokyo); 29(11):3311-3319 1981

Purified alpha-fetoprotein (AFP) messenger (m)RNA from rat AH-66 hepatoma cells formed complementary (c)DNA upon incubation in a system with avian myeloblastosis virus RNA-dependent DNA polymerase. The (3H)cDNA had a peak fraction of about 1,000 nucleotide length upon alkali-sucrose gradient centrifugation; AFP cDNA hybridized with AFP mRNA, but not with rat liver catalase mRNA. Thermal denaturation analysis showed a sharp melting profile, indicating a faithful transcription in AFP cDNA:mRNA hybrids. The conformation of the AFP gene was studied by digestion of nuclei of AH-66 cells and rat liver cells with DNAse I or microsomal nuclease. Chromosomal proteins (CP) extracted from chromatin of AH-66 and rat liver cells were similar in comparisons by QAE-Sephadex A-25 chromatography and sodium dodecyl sulfate-polyacrylamide gel electrophoresis. RNA transcripts from intact and reconstituted chromatin of AH-66 cells hybridized with AFP cDNA, but those from rat liver cells did not, indicating that AFP gene is active in AH-66 cells, but suppressed in liver cells. The addition of one of the fractions of AH-66 CP during reconstitution of rat liver chromatin lead to transcription of the AFP gene; no rat liver CP could be found that when added during reconstitution would inhibit transcription of AH-66 AFP gene. (24 Refs)

11. TRANSFORMED CELLS EXHIBIT ALTERED RESPONSE TO DB CYCLIC AMP-MEDIATED MODULATION OF PROTEIN PHOSPHORYLATION AND DIFFERENT ENDOGENOUS PHOSPHOPROTEIN ACCEPTORS.

Rieber MS, Rieber M
(c/o Rieber) Center Microbiology and Cell Biology, Inst. Venezolano de Investigaciones Centrificas, Apartado 1827, Caracas 1010-A, Venezuela
Cancer Biochem Biophys; 5(3):163-167 1981

Detergent solubilized particulate fractions (DSF) and cytoplasmic fractions (CF) derived from NRK cells transformed with the temperature-sensitive ts24 derivative of Rous sarcoma virus and grown at 33 C (malignant phenotype) and 39 C (normal phenotype) were compared. Protein kinase activities were in the following order: DSF, transformed greater than or equal to DSF, phenotype normal greater than or equal to CF, transformed greater than or equal to CF, phenotype normal. Incubation of CF of morphologically normal cells grown for 48 hr at 39 C with ATP-gamma-32P led to phosphorylation mostly in components of 60,000 and 68,000 daltons; in vitro exposure of extracts to dibutyryl cyclic AMP increased labeling of the 60,000 dalton component and decreased labeling in the 68,000 dalton component. A similar experiment with CF of phenotypically transformed cells grown at 33 C yielded 140,000 and 38,000 dalton components, both of which showed decreased labeling when the experiment was repeated with cyclic AMP preincubation. DSF of phenotypically normal cells labeled preferentially in 38,000, 65,000, and 94,000 dalton regions, and these preferences did not change with cyclic AMP. DSF of phenotypically transformed cells labeled mainly in the 65,000 dalton region; with cyclic AMP preincubation the 65,000 dalton labeling decreased and labeling increased in the 220,000 dalton region. Failure of transformed cells to phosphorylate some substrates may be due to a transformation-induced alteration in the availability of endogenous protein acceptors for the phosphorylation process, and not to a low level of protein kinase activity. (13 Refs)

12. DECREASED UPTAKE AND RETENTION OF RHODAMINE 123 BY MITOCHONDRIA IN FELINE SARCOMA VIRUS-TRANSFORMED MINK CELLS.

Johnson LV, Summerhayes IC, Chen LB
Dept. Anatomy, Sch. Medicine, Univ. Southern California, 2025 Zonal Ave., Los Angeles, CA, 90033
Cell; 28(1):7-14 1982

A reduced uptake and retention of the mitochondria-specific membrane potential probe rhodamine 123 by feline sarcoma virus (FeSV)-transformed mink fibroblasts (64F3) has been detected. The decreased accumulation of rhodamine 123 by 64F3 mitochondria is not due to abnormal plasma membrane dye permeability, since after microinjection of the dye these cells are still unable to retain the dye at levels comparable to the untransformed parental cells, CCL 64. Nigericin, an ionophore that mediates an electrically neutral exchange of protons of potassium ions resulting in the elimination of the pH gradient across the mitochondrial membrane and a compensatory increase in mitochondrial membrane potential with continued respiration, increases both the dye uptake and the retention time in transformed 64F3 cells. These results suggest that mitochondria in FeSV-transformed mink cells may have an abnormally low mitochondrial membrane potential accompanied by a relatively high pH gradient. Since anionic metabolites such as pyruvate and glutamate are accumulated by mitochondria in proportion of the deltapH across the mitochondrial membrane, the abnormal mitochondria described here may contribute to the abnormal metabolic state of FeSV-transformed cells. (Author abstract) (26 Refs)

13. ELECTRON SPIN RESONANCE OF GROWING NORMAL AND VIRUS-TRANSFORMED CELLS.

Conti F, Segre AL, Eremenko T, Zaniratti S, Elia G, Benedetto A, Volpe P
Inst. Physical Chemistry, Univ. Rome, Rome, Italy
Cancer Biochem Biophys; 5(3):195-199 1981

A g = 2.003 electron spin resonance (ESR) signal, previously detected in association with a free radical in HeLa cells, was analyzed in fractionated HeLa cells and whole cell cultures of mouse embryo 3T3 fibroblasts transformed by Simian virus 40 (SV40) and in normal rabbit kidney (NRK) cells transformed by Rous sarcoma virus (RSV). The g = 2.003 ESR signal was localized in the mitochondria and nuclei of HeLa cells and had the same shape in both compartments as in whole cells; no signal was detected from cytoplasmic and membranal compartments. In the other cell lines the signal was maximal in intensity in the lag stage but reduced thereafter; in 3T3 and 3T3/SV40 cells the maximal value occurred early in the lag stage. The max signal occurs late in the lag phase in NRK and NRK/RSV cells. Specific intensity of the g = 2.003 ESR signal per cell is significantly higher in 3T3 and 3T3/SV40 cells than in NRK and NRK/RSV cells. Av specific intensity of the ESR signal over the whole culture period is higher in normal cells of both lines, but the maximal point of resonance per cell during the lag stage is higher in the transformed cells. The role of free radicals as triggers in cells grown in vitro is discussed. (10 Refs)

14. MORPHOLOGICAL TRANSFORMATION OF CELLS INDUCED BY KIRSTEN SARCOMA VIRUS TRANSFORMING FACTOR IS INDEPENDENT OF SERINE PROTEASES.

Fulton RJ, Kaplan PL, Hart DA, Ozanne B
(c/o Ozanne) Dept. Microbiology, Univ. Texas Health Science Center at Dallas, Dallas, TX, 75235
J Cell Physiol; 110(1):81-83 1982

Kirsten murine sarcoma virus (MSV)-induced cell transformation is thought to be regulated by a low mol wt peptide growth factor(s) known as transforming factor (TF) which is extractable from MSV-transformed NRK cells' conditioned medium. A caseinolytic assay was used for detection of neutral protease and plasminogen activator (PA) activities in extracted TF and in fully-transformed Rat-1 cells which had been treated with TF. Neither the isolated TF nor the cultures of Rat-1 cells showed elevated protease or PA activities; neutral proteases and PA evidently do not play a role in the morphological transformation induced by TF. (15 Refs)

15. GENERAL INHIBITION OF EMBRYONIC CELL AGGREGATION BY NEOPLASTIC CELLS.

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Dept. Experimental Pathology, Roswell Park Memorial Inst., Buffalo, NY, 14263

Cancer Lett; 15(2):167-171 1982

The inhibitory action of malignant cells on aggregation and adhesion of chick embryo skeletal muscle, heart, and liver cells was examined. Mean aggregate diameters formed by muscle, heart, and liver cells were significantly reduced in the presence of 1 x 10(5) Ehrlich ascites Lettre' hyper diploid (ELD) cells. The numbers of adherent muscle, heart, and liver cells after 2 or 4 hr incubation with ELD cells at an embryonic/ELD cell ratio of 50:1 were significantly greater than those of control cultures. Addition of cell-free conditioned medium in which ELD cells had grown resulted in 37%, 50%, and 12% reduction in the sizes of aggregates formed by muscle, liver, and heart cells, respectively. The presence of Rous sarcoma virus-transformed chick embryo neural retina cells (60 untransformed cells:1 transformed cell) resulted in a 37% reduction in aggregate size. Aggregation inhibition in embryonic cells, like that previously reported for neural retina cells, can be considered a general response of non-cancer cells specifically to the presence of cancer cells. (8 Refs)

16. SPECIFIC DIFFERENTIATION EVENTS INDUCED BY ERYTHROPOIETIN IN CELLS INFECTED IN VITRO WITH THE ANEMIA STRAIN OF FRIEND VIRUS.

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Proc Natl Acad Sci USA; 79(2):635-639 1982

Mouse bone marrow cells infected in vitro with the anemia strain of Friend leukemia virus form large clusters (bursts) of erythroblasts after 5 days in culture in methylcellulose medium. Two types of erythroblast populations can be isolated from bursts of infected cells by manipulation of the culture conditions. One type of erythroblast, which is obtained when erythropoietin (EP) is added to the culture, has proliferated and undergoes differentiation to become an erythrocyte. The second type of erythroblast, which is obtained when no EP is added to the culture, is the product of extensive proliferation, but it fails to undergo the terminal stages of erythroblast differentiation. Comparisons of these two types of erythroblasts demonstrate that specific EP effects include changes in the nucleus, cytoplasm, and membrane of the treated cells. Those events of erythroid differentiation shown to be directed by EP were extrusion of the nucleus from the erythroblast, induction of uroporphyrinogen I synthetase activity, increased iron incorporation into protoporphyrin, synthesis of alpha- and beta-globin polypeptides due largely to increased mRNA production, and synthesis and incorporation of spectrin into the cell membrane. In this system, EP promotes these effects without observable stimulation of progenitor proliferation in addition to that caused by the virus alone. Thus, the role of EP in terminal erythrocyte differentiation is not simply that of an erythroid-specific mitogen. (Author abstract) (30 Refs)

17. THE MYELOPROLIFERATIVE SARCOMA VIRUS CAUSES TRANSFORMATION OF ERYTHROID PROGENITOR CELLS IN VITRO.

Hankins WD, Kost TA, Pragnell IB
(c/o Pragnell), Beatson Inst. for Cancer Res., Bearsden, Glasgow, G61 1BD, Scotl and
Mol Cell Biol; 2(2):138-146 1982

In vitro transformation of mouse erythroid progenitor cells by myeloproliferative sarcoma virus (MPSV) was studied. Anemia was induced in male BALD/c, DBA/2J, C57BL/6, and CD2F1 mice by injection of phenylhydrazine hydrochloride (PHZ: 40 ug/g, days 1, 2 and 4). Bone marrow or spleen cells from PHZ-treated mice were cultured with or without erythropoietin (EPO: 0.2 units/ml). The presence of Hb was measured by benzidine staining. Cultures treated with EPO showed a transient increase in Hb-containing cells at days 2-3, lysis of erythroid cells on day 4, and few, if any, erythroid cells by day 5. Cultures infected with MPSV without EPO showed a few erythroid bursts (EB) on days 5-9. Addition of 0.1 unit EPO/ml to MPSV-infected cultures resulted in a significant increase in EB. The number of EB was related to the amount of virus present during absorption. MPSV induced EB in spleen cells from all mouse strains tested, with greatest effect on CD2F1 cells. The greatest numbers of EB were present on days 6-8 after infection. Predominant cell fractions consisted of large proerythroblast-like cells on days 3-5, smaller Hb-containing cells on days 6-7, and nucleated erythrocytes and reticulocytes on days 8-10. Assays using a number of factors indicated that EB-inducing activity was produced by MPSV, rather than by a soluble factor. The activity was eliminated by heat treatment or sedimentation. (33 Refs)

18. STUDIES OF CAUSAL CORRELATIONS AND PATHOGENESIS OF LEUKOSIS, NEPHROBLASTOMAS, OVARIAN TUMORS, AND OSTEOPETROSIS AFTER INFECTION WITH AVIAN LEUKOSIS VIRUSES.

Loliger HC, Von dem Hagen D, Hartmann W
Institut fur Kleintierzucht, D-3100 Celle, W. Germany
DTW; 89(1):22-28 1982

Correlations between infection with avian leukosis viruses and appearance of leukosis (LK), nephroblastomas (NB), ovarian tumors (OT), and osteopetrosis were studied. Several lines of chickens with varying viral sensitivities were infected with avian myeloblastosis virus (AMV), avian erythroblastosis virus (AEV), or Marek herpes virus (MHV). Pathological conditions developed in chickens susceptible to A- or B-group avian leukosis viruses (ALV) but not in resistant chickens. Pleiomorphic diseases developed in chickens infected with AMV but not in chickens infected with MHV or AEV. MHV induced only monomorphic lymphoreticular neoplasias; induction was independent of the stage of genetic susceptibility. The incidence of pathological conditions decreased as the age of chickens at the time of infection increased. In older chickens leukemia appeared only as acute, early stages of disease. Occurrence of leukemia was related to the concentration of virus introduced. Nephroblastomas and cystadenomas appeared as late effects of viral infection and increased in frequency as the frequency of acute leukemia decreased. Osteopetrosis develop ed in all lines susceptible to AMV, particularly in dysgammaglobulinemic lines. No association of nephrogenic or osteogenic tumor factor with viruses of subgroup A or B was demonstrated. Results indicate that the targets of AMV are pluripotential embryo-reticular cells and undifferentiated hemoblast present only in newly hatched chicks, and that the viruses act by blocking cellular differentiation. (25 Refs) (In GER)

19. EFFECT OF BENZO[A]PYRENE ON FRIEND VIRUS LEUKEMOGENESIS, CFU-S VIABILITY, AND INDUCTION OF HUMORAL IMMUNITY.

Raikow RB, OKunewick JP, Buffo MJ, Jones DL
Cancer Res. Lab., Allegheny-Singer Res. Corp., Allegheny General Hosp., Pittsburgh, PA, 15212
Experientia; 38(1):126-127 1982

The compound benzo[a]pyrene (BP) potentiated the induction of leukemia by low doses of Friend virus in SJL/J mice if injected 2 days before the virus. BP also reduced the viability of hematopoietic stem cells (CFU-S) within this time interval but had little effect on the induction of humoral immunity (the PFC response). (Author abstract) (18 Refs)

20. ASSOCIATION OF LYMPHOID LEUKOSIS VIRUS AND PERFORMANCE IN A RANDOMBRED LAYER POPULATION.

Garwood VA, Okazaki W, Crittenden LB, Lowe PC
North Central Regional Poultry Breeding Lab., Purdue Univ., West Lafayette, IN, 47907
Poult Sci; 60(12):2619-2621 1981

The performance of group specific (gs) antigen shedders and gs nonshedders was investigated in the North Central Randombred population developed from White Leghorn chickens. Of 429 females tested with the complement fixation test, 102 were shedders and 327 nonshedders. Thus lymphoid leukosis virus was present in 23.8% of the population. Superior performance was found in nonshedders, indicated by earlier maturation, more egg production, larger eggs, and increased body wt. (13 Refs)

21. SKELETAL HYPEROSTOSES. VIRAL INDUCTION OF AVIAN OSTEOPETROSIS.

Schmidt EV, Smith RE
Dept. Microbiology and Immunology, Duke Univ. Medical Center, Durham, NC
Am J Pathol; 106(2):297-299 1982

Virus-induced avian osteopetrosis is useful for studies related to the growth of osteoblasts, the molecular signals in the host cell that cause the proliferation of osteoblasts, and the immune parameters that permit abnormal cell growth. An abnormal proliferation of osteoblasts is common to certain human diseases, the most fatal of these being osteosarcoma, and also is some evidence for a viral origin of human osteosarcomas. (15 Refs)

22. POTENTIAL IDENTIFICATION OF CHEMICAL CARCINOGENS IN A VIRAL TRANSFORMATION SYSTEM.

Wilson WW, Khoobyarian N
(c/o Khoobyarian) Dept. Microbiology and Immunology, Sch. Basic Medical Sciences, Univ. Illinois at Medical Center, P.O. Box 6998, Chicago, IL, 60680
Chem Biol Interact; 38(2):253-259 1982

Chemical carcinogens from several diverse chemical classes ie; aromatic amines, polycyclic hydrocarbons, nitrosamines, hormonal derivatives, metals and direct alkylating agents cause a 6.2-60.5-fold increase in the frequency of murine sarcoma virus (MSV)-induced transformation in a normal rat kidney (NRK) cell system. Exogenous metabolic activation with a rat liver S-9 homogenate is required for expression of this activity by procarcinogens. Non-carcinogenic analogs of these compounds fail to cause significant increases in the transformation frequency either with or without prior metabolic activation. Iododeoxyuridine, a mutagen also does not cause enhancement of transformation. This system may serve as the basis for a rapid and quantifiable means of identifying chemical carcinogens while introducing a new model for the understanding of the interactions between oncornaviruses and chemical carcinogens. (Author abstract) (14 Refs)

23. ONCOGENIC VIRUSES AND CELLULAR TRANSFORMATION.

Ruggiero R, Dosne de Pasqualini C
Departamento Leucemia Experimental, Instituto de Investigaciones Hematologicas, Academia Nacional de Medicina, Buenos Aires, Argentina
Bol Acad Nac Med; 59:117-127 1981

Oncogenic viruses (OV) and cellular transformation (CT) were reviewed under the following headings: characteristics of oncogenesis due to virus, types of OV, life cycle of Rous sarcoma virus (RSV), genome of RSV, transformation gene (src), transformation protein (TP) of src gene, and location of action of the phosphoprotein TP with mol wt 60,000. (20 Refs) (In SPA)

VIRUS REPLICATION AND EXPRESSION

24. RESTRICTED EXPRESSION OF INTEGRATED PRIMATE TYPE-C VIRUS (GIBBON APE LEUKEMIA VIRUS-SIMIAN SARCOMA VIRUS) PROVIRAL DNA IN NONPRODUCTIVELY INFECTED HUMAN B LYMPHOBLASTS.

Ceccherini Nelli L, Dalla-Favera R, Markham PD, Ruscetti FW, Wong-Staal F, Gallo RC, Reitz MS
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Virology; 117(1):195-206 1982

Human B-lymphoblast cell lines established from peripheral blood after infection with retroviruses of the simian sarcoma/simian sarcoma associated virus (SSV/SSAV)-gibbon ape leukemia virus (GALV) group generally do not produce detectable virus, even though viral RNA and protein are expressed. We show here by Southern blot and liquid molecular hybridization experiments that most of these nonproducer cultures not producing virus contain apparently complete proviral DNA sequences which lack detectable rearrangements, indicating that restriction of virus replication is not due to obvious proviral lesions. The provirus is often present in only a fraction of the cell population, although the proviral copy number is variable and increases during extensive tissue culture or passage through nude mice. The proviral DNA is integrated into multiple heterogeneous sites in these cells, indicating a polyclonal population. A few of these cell lines have been cloned. Clonal lines have so far originated only from cells which contain proviral DNA and express viral RNA, although they still do not produce complete or infectious virus. Southern blots show that these cells are clonal in origin and contain a complete provirus with two LTRs arranged in the normal orientation. Two viral mRNA species are expressed which are identical in size to those from virus-producing cell lines. The smaller (presumably env) mRNA, like that from virus-producing lines is a spliced transcript which contains both 5'- and 3'-derived sequences. These data strongly suggest that these cells restrict viral replication at some stage later than mRNA synthesis, possibly at the level of protein synthesis or processing. (Author abstract) (15 Refs)

25. ENDOGENOUS MURINE LEUKEMIA VIRUS-ENCODED PROTEINS IN RADIATION LEUKEMIAS OF BALB/C MICE.

Tress E, Pierotti M, DeLeo AB, O'Donnell PV, Fleissner E
(c/o Fleissner), Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Virology; 117(1):207-218 1982

To explore the role of endogenous retroviruses in radiation-induced leukemogenesis in the mouse, we have examined virus-encoded proteins in nine BALB/c leukemias by pulse-chase labeling procedures and serological typing with monospecific and monoclonal antibodies. The major gag precursor protein, Pr65gag, was observed in all cases, but only three leukemias expressed detectable amounts of the glycosylated gag species, gP95gag, or its precursor, Pr75gag. No evidence was found for synthesis of gag-host fusion proteins. None of the leukemias released infectious xenotropic or dualtropic virus, but all nine expressed at least one env protein with xenotropic properties. In two instances a monoclonal antibody, 35/56, which is specific for the MuLV GIX antigen, displayed a distinctive reactivity with this class of env protein, although this antibody is unreactive with replicating xenotropic viruses. An ecotropic/xenotropic recombinant env protein with the same 35/56 phenotype was observed in a leukemia induced by a strongly leukemogenic virus isolated from a BALB/c radiation leukemia. (Author abstract) (40 Refs)

26. MAMMARY TUMOR VIRUS (MTV) ANTIGEN EXPRESSION IN MALE GENITAL ORGANS FROM VARIOUS INBRED STRAINS OF MICE.

Imai S, Morimoto J, Tsubura Y
Second Dept. Pathology, Nara Medical Univ., Nara, Japan
Nara Igaku Zasshi; 32(5):570-573 1981

In an effort to demonstrate the route of extrachromosomal male transmission of MTV, MTV antigen expression in the epididymis and coagulating glands of the male genitalia of various strains of inbred mice was investigated with the aid of micro-immunodiffusion (micro-ID) test. The MTV expression was studied in the following strains of mice: high mammary cancer strains (GR, DD/Tbr, SHN, SLN, C3 H/HeA), intermediate mammary cancer strains (DDD and KF), and low mammary cancer strains with low and moderate incidence of leukosis (but including AKR/RU). In the mice with positive micro-ID tests, the frequency of MTV antigen expression was generally lower in the epididymis than in the coagulating gland. The frequency of MTV antigen expression also depended on the mouse strains; high mammary cancer strains showed more frequent antigen expression in the male genital organs than low mammary cancer strains showed. Overall, there was no marked difference with regard to the frequency of antigen expression among the high mammary cancer strains. These findings confirmed that the male genitalia play an important role in paternal transmission of MTV. (17 Refs)

27. INHIBITION OF THE RELEASE OF VIRION-ASSOCIATED MURINE LEUKEMIA VIRUS GENOMIC RNA BY VESICULAR STOMATITIS VIRUS.

Chan JC, Mohr MD, Knesek JE, Bowen JM, East JL
Dept. Molecular Carcinogenesis and Virology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Intervirology; 16(3):191-200 1981

The genomic RNAs of murine leukemia virus (MuLV) and vesicular stomatitis virus (VSV) were distinguishable based on a difference in sedimentation coefficient, polyadenylic acid content, and nucleotide sequence homology. Applying these biochemical characteristics, we found that the release of virion-associated MuLV genomic RNA from virus-producing cells was inhibited by VSV as early as 2 hr after superinfection. This finding offers an explanation to our previous inability to detect MuLV (VSV) pseudotype formation during mixed infection with VSV and MuLV. (Author abstract) (39 Refs)

28. TWO DISTINCT INTRACELLULAR PATHWAYS TRANSPORT SECRETORY AND MEMBRANE GLYCOPROTEINS TO THE SURFACE OF PITUITARY TUMOR CELLS.

Gumbiner B, Kelly RB
Dept. Biochemistry and Biophysics, Univ. California, San Francisco, San Francisco, CA, 94143
Cell; 28(1):51-59 1982

The pituitary cell line, AtT-20, synthesizes adrenocorticotropic hormone (ACTH) as a glycoprotein precursor that is cleaved into mature hormones during packaging into secretory granules. The cells also produce an endogenous leukemia virus (MuLV) that is glycosylated after translation similar to the glycosylation of the ACTH precursor. Our evidence suggests that the envelope glycoprotein and some precursor ACTH get to the cell surface in a vesicle different from the mature ACTH secretory granule. Viral glycoproteins and ACTH precursor are released from the cells much sooner after synthesis than mature ACTH. Isolated secretory granules do not contain significant amounts of the envelope glycoprotein or ACTH precursor. Exposing cells to 8Br-cAMP stimulates release of mature ACTH four to five fold, but has little effect on the release of the ACTH precursor or the viral glycoproteins. We propose that the viral glycoproteins and some of the ACTH precursor are transported by a constitutive pathway, while mature ACTH is stored in secretory granules where its release is enhanced by stimulation. (Author abstract) (32 Refs)

29. EFFECT OF PH ON FLUORESCENCE POLARIZATION OF DMSO INDUCED FRIEND LEUKEMIC CELLS.

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Cancer Biochem Biophys; 5(3):147-152 1981

Membranes of Friend leukemic cells (FLC) derived from clone 745A of Friend virus transformed cells were studied by diphenyl hexatriene (DPH) fluorescence polarization at pH 4.5, 7.0 and 9.0. Fluorescence polarization values (P) of artificial phosphatidyl choline and phosphatidyl choline/cholesterol liposomes did not change with pH, but when growing FLC and a variant FLC strain (RFLC) resistant to dimethyl sulfoxide (DMSO: 280 milliMoles) induced globin synthesis were analyzed in the same way, P-values increased with pH, but in different ways for different cell lines. The differences were much greater when cells had been treated with DMSO, which induced erythroid differentiation (75% of FLC benzidine dihydrochloride (B) positive on 4th day; less than or equal to 1% of RFLC B+ under same conditions). In both FLC and RFLC, P-value changes related to pH were abolished with 2.5 % glutaraldehyde inhibition of the fluid state of cell membranes and by sodium azide inhibition of the cellular energy generating system. At 4 C, P-values for untreated FLC varied according to pH to the same extent as at 37 C, but DMSO-induced FLC and both untreated and DMSO-treated RFLC exhibited no P-values changes at the lower temperature. P-values could be restored in these cells by raising temperature to 37 C. P-value changes of DPH-labeled FLC reflect lipid-protein interactions; DMSO induction alters these interactions. (28 Refs)

30. ASSOCIATION OF MOLONEY MURINE LEUKAEMIA VIRUS PROTEINS: AN ASSAY FOR HYDROPHOBIC PROTEIN-PROTEIN INTERACTIONS.

Andersen KB
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J Gen Virol; 58(part1):83-93 1982

Protein-protein interaction of Moloney murine leukemia virus was studied by an assay where one protein preparation was coupled covalently to Sepharose, and binding of radiolabeled proteins to the protein-Sepharose was examined. It was found that the virus proteins gp70, p30, p15E and p15 in solution could associate weakly to disrupted virus particles and to p30. However, when the disrupted virus particles and p30 were coupled to Sepharose in the presence of Triton X-100, stronger binding of the four proteins was observed. Only low or no binding of p12 and p10 was observed to these protein-Sepharoses. The results are discussed with respect to the assembly and structure of the virus particle. (Author abstract) (33 Refs)

31. MOUSE MAMMARY TUMOUR VIRUS AND POLYOMA VIRUS INFORMATION IN MAMMARY TUMOURS OF ATHYMIC MICE INOCULATED WITH POLYOMA VIRUS.

Arya SK, Galarraga JJ
Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20205
J Gen Virol; 58(part1):107-114 1982

Polyoma virus inoculation of athymic mice results in the development of mammary tumors with a much higher incidence than the development of salivary gland tumors, the latter being the most common for immunocompetent normal mice. The possibility existed that polyoma virus might act as a co-carcinogen in activating the expression of mouse mammary tumor virus (MMTV). Molecular hybridization studies, however, showed that the mammary tumor development was accompanied by neither the amplification of MMTV genomic sequences nor by their more extensive transcription. In contrast, tumor tissue contained about 60 to 100 copies of polyoma virus genome equivalents per cell and some of these sequences were apparently transcribed into RNA. While these results do not rule out the transient involvement of MMTV expression in mammary tumor development, it appeared that the mammary gland cells were directly transformed by polyoma virus. Apparently, polyoma virus displayed a tropism in athymic mice that was different from that in normal mice. (Author abstract) (30 Refs)

32. CONTRIBUTION TO EPIDEMIOLOGIC STUDIES OF BOVINE ENZOOTIC LEUKOSIS.

de Alencar RA, Rodrigues FM, Vianna WO
Instituto Biologico, Sao Paulo, Brazil
Biologico; 47(9):249-253 1981

An epidemiologic study of bovine enzootic leukosis (BLV) was performed, using cohabitation (CO), feeding (FE), or blood transfusion (BT). The BT experiment consisted of transferring 200 ml of blood from two serologically positive animals into two that were serologically negative. Immunodiffusion tests (IDT), performed on days 30, 60, 90, 120, and 180, using antigen Leukassay-B, all gave negative results. Eleven cows that were clinically negative for bovine leukemia virus (BLV) showed positive results with the IDT for blood, three showed positive results for colostrum 24 hr after delivery, and five for colostrum 48 hr after delivery. Blood of three of their heifers gave positive results 24 hr after birth and five gave positive results 48 hr after birth; 6 mo later none of the heifers gave positive results. The CO and FE of serologically positive or negative heifers for BLV and of cows that were serologically positive but clinically negative, did not endanger the heifers. Cross reaction was not observed between serum containing antibodies for BLV and serum containing antibodies for bovine diarrhea virus. (5 Refs) (In POR)

GENETICS

33. GENETIC MAPPING OF ECOTROPIC MURINE LEUKEMIA VIRUS-INDUCING LOCI IN SIX INBRED STRAINS.

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J Exp Med; 155(2):524-534 1982

Mendelian segregation analysis was used to map chromosomal genes for the induction of endogenous N- and B-tropic ecotropic retroviruses (V loci) in high and low leukemic mouse strains. Segregation analysis resulted in the genetic mapping of V loci in six inbred strains to five mouse chromosomes. The V locus of A/J was mapped to chromosome 5 and shown to be allelic with that of BALB/cJ and C3H/HeJ (Cv); this suggests that Cv represents a stable ancestral V locus present in Bagg albino stocks before separation of inbred lines. The single, poorly inducible V locus of C57BL/10J and one of the four high virus loci of C58/Lw were mapped to the same region of chromosome 8 and may present an allelic pair with different patterns of expression. An N-tropic V locus of the SEA/GnJ mouse was mapped to chromosome 9, and one of the three V loci of C3H/FgLw was mapped to chromosome 7. The endogenous B-tropic virus of B10.BR/SgLi was mapped to chromosome 11. Several of the endogenous proviral sequences appear to be closely linked with cellular genes involved with sensitivity or resistance to retroviral infection or affecting lymphoid differentiation. Identification and separation of individual V loci aids in their characterization and makes it possible to identify DNA fragments carrying biologically defined proviruses. (26 Refs)

34. THE SAME GENETIC LOCUS DIRECTS DIFFERENTIATION-LINKED EXPRESSION OF ENDOGENOUS RETROVIRUS GP70 ON THYMOCYTES AND SPLEEN CELLS IN THE MOUSE.

Tung JS, Shen FW, Viamontes G, Palladino M, Fleissner E

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Immunogenetics; 15(1):103-108 1982

Expression of the major envelope glycoprotein (gp70) of murine leukemia virus (MuLV) was studied in spleen cells of C57BL/6 (B6) and 129 mice that are negative for thymocytes surface antigen (GIX) and spleen cells of their congeneic GIX+ and GIX- derivatives. Proteins with a mol wt of approx 70,000 daltons were specifically recognized by a group-specific anti-gp70 serum in spleen cell lysates of 129, B6, and B6-GIX+ mice; 129-GIX- cells were negative. A monoclonal antibody specific for GIX+ MuLV gp70 precipitated the same gp70 molecules on spleen cells from the GIX+ strains. Occurrence of spleen cell gp70 in these strains appeared to controlled by the same genetic locus (Gv-1) that determines the presence of GIX+ gp70 on thymocytes. The presence of gp70 on spleen cells from B6-nu mice as well as on cytotoxic spleen T cells indicated that gp70 molecules are expressed by both T and non-T cells. (15 Refs)

35. CHARACTERIZATION OF XENOTROPIC AND DUAL-TROPIC TYPE C RETROVIRUSES ISOLATED FROM ABELSON TUMOUR.

Chang KS, Log T, Bandyopadhyay AK

Viral Oncogenesis Section., Lab. Cell Biology, NCI, Bethesda, MD, 20205

J Gen Virol; 58(part1):115-125 1982

Tumors induced in Balb/c mice by Abelson virus complex were found to contain a xenotropic virus (A-X-MuLV) and an NB-tropic, dual-tropic virus (NBX), in addition to the Moloney leukemia virus (M-MuLV) and the defective, transforming Abelson virus genome. Both A-X-MuLV and NBX virus were presumably present in a genomically masked form and could be recovered only by co-cultivation of tumor cells with permissive cells. Only about 0.87% and 0.13% of the viruses in the co-culture supernatant represented A-X-MuLV and NBX virus respectively; the majority were M-MuLV. The NBX virus acted more efficiently than the HIX virus as helper to rescue murine sarcoma virus (MSV) from S+L- cells of hamster, rat and mouse origin, whereas the converse was true for those of cat and human origin. The interference and neutralization patterns suggested that the NBX virus was an env gene recombinant between A-X-MuLV and M-MuLV. The fact that NBX virus cross-reacted in radioimmunoassays with gp70s of both M-MuLV and Balb:virus-2 provides evidence for the recombinant nature of the NBX gp70-coding gene which was probably derived from both M-MuLV and a virus similar to Balb:virus-2 or A-X-MuLV. The presence of a unique antigenic determinant on the gp70 of NBX virus is also suggested. Both A-X-MuLV and NBX virus cross-reacted with type-specific p12s of M-MuLV and Balb;virus-2, suggesting that the gag gene coding for p12 of NBX virus was derived from the A-X-MuLV, which was itself a recombinant, its p12-coding gene being derived from both Balb:virus-2-like virus and M-MuLV. The NBX virus was not oncogenic when tested in newborn Balb/c mice. (Author abstract) (40 Refs)

36. GENETIC CONTROL OF SENSITIVITY TO MOLONEY LEUKEMIA VIRUS IN MICE: V. ROLE OF H-2-LINKED GENES IN THE CONTROL OF ANTI-FMR CYTOLYTIC T-LYMPHOCYTES.

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Cell Immunol; 65(2):317-324 1981

Three H-2-linked genes, Rmv1, Rmv2, and Rmv3 control the resistance of mice against Moloney virus (MLV)-induced leukemias. It has been shown previously that they function as immune response (Ir) genes regulating the level of antivirus antibodies. In the present experiments, the cell-mediated antitumor response has been studied in a series of inbred strains selected for their resistance or sensitivity to the MLV-induced disease. We failed to detect any relationship between resistance and sensitivity and the ability to produce cytolytic T lymphocytes (CTL) directed against the virus-induced FMR cell surface antigen. Furthermore, the role of each Rmv gene has been studied separately using congenic pairs of mice differing at only one of these loci: we failed to evidence any influence of these genes in the cell-mediated antitumor reactions as measured by the ability to lyse syngeneic FMR(+) target cells. Nevertheless a gene mapping in the D region of the MHC but probably different from RMv3 controls the response of a subset of anti-FMR CTL restricted by the H-2Kk antigens, with higher response in H-2Dd animals than in H-2Db animals. This observation confirms the existence of H-2D region associated Ir genes regulating the CTL-mediated antitumor immune responses by choosing the subset of responder CTL, and suggests that a fourth H-2-linked gene plays some role in the genetic control of the anti-FMR immune response. (Author abstract) (15 Refs)

37. PHOSPHORYLATION OF A 36,000 MR CELLULAR PROTEIN IN CELLS INFECTED WITH PARTIAL TRANSFORMATION MUTANTS OF ROUS SARCOMA VIRUS.

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(c/o Weber) Dept. Microbiology, Univ. Illinois, Urbana, IL, 61801

Mol Cell Biol; 2(2):147-153 1982

Correlation of parameters of transformation with phosphorylation of the phosphoprotein pp60src in cell infected with mutants of Rous sarcoma virus (RSV) was studied. Chick embryo fibroblasts were infected with viruses derived from the Schmidt-Ruppin strain of RSV, subgroup A. Viruses tested included wild-type (WT), temperature-conditional mutants (tsGI251, tsCU11, and tsNY68), CU2 mutant, and fusiform CU12 mutant. The mutant strains induced some, but not all, parameters of cellular transformation. The 36,000 mol wt pp60src from uninfected fibroblasts showed little or no phosphorylation. Equivalent pp60src from RSV-infected fibroblasts showed phosphorylation. Phosphorylation was temperature-conditional in cells infected with tsNY68, tsCU11, and tsGI251. Cells infected with CU2 showed a low degree of phosphorylation. Pp60src from RSV-infected cells was phosphorylated with tyrosine and serine, phosphotyrosine being predominant. Analysis of phosphorylation and occurrence of transformation parameters showed that phosphorylation of pp60src was neither sufficient nor necessary for loss of surface fibronectin or loss of density-dependent inhibition of growth. Phosphorylation was not sufficient but was possibly required for changes in morphology. Phosphorylation was not sufficient for loss of adhesiveness or full increase in hexose transport.

Phosphorylation correlated well with increase in plasminogen activator. Results suggest that phosphorylation of pp60src may be required for malignant growth. (23 Refs)

IMMUNOLOGICAL STUDIES

38. T CELL TOLERANCE IN MOLONEY-MURINE LEUKEMIA VIRUS (M-MULV) CARRIER MICE: LOW CYTOTOXIC T LYMPHOCYTE PRECURSOR FREQUENCY AND ABSENCE OF SUPPRESSOR T CELLS IN CARRIER MICE WITH MOLONEY-MURINE SARCOMA (M-MSV)-INDUCED TUMORS.

Collavo D, Ronchese F, Zanovello P, Biasi G, Chieco-Bianchi L
Lab. Oncology, Inst. Pathological Anatomy, Univ. Padova, Padova, Italy
J Immunol; 128(2):774-779 1982

Mice neonatally injected with Moloney-murine leukemia virus (M-MuLV) become permanent virus carriers and, in contrast to normal mice, fail to reject Moloney-murine sarcoma virus (M-MSV)-induced tumors as adults (progressor mice). Failure of tumor rejection has been shown to correlate with lack of T cell responsiveness of lymphoid cells from carrier mice in terms of tumor-specific cytotoxic T lymphocyte (CTL) generation in vitro and with failure to transfer protection against tumor growth in T cell-deficient mice. Since, in addition, lymphoid cells of carrier mice failed to suppress CTL generation in vitro by M-MSV-immune spleen cells, it was concluded that neonatal M-MuLV injection resulted in a state of T cell tolerance. Recent reports have suggested that carrier mice injected with M-MSV (progressor mice) generate suppressor cells that mediate enhanced tumor growth and inhibit CTL generation in vitro. In the present report, we fail to confirm these findings by demonstrating the following: (a) Neither carrier nor progressor spleen cells suppress the tumor protective effect of M-MSV-immune cells in T-deficient mice. (b) Progressor spleen cells fail to suppress M-MuLV-specific CTL generation by immune cells. (c) Spleens of carrier mice contain 100-fold lower M-MuLV-specific CTL precursors than do spleens of normal mice, and spleens of progressor mice contain over 1,000-fold lower CTL-precursor frequencies than do spleens of regressor mice. (d) Spleen cells from progressor mice fail to inhibit the clonal response of small numbers of CTL precursors in micro-mixed leukocyte tumor cell cultures. Thus, these results support the hypothesis that M-MSV tumor progression in carrier mice is due to reduction in virus-specific CTL precursor frequency and not to the generation of suppressor cells. (Author abstract) (36 Refs)

39. IMMORTALIZATION OF ANTIGEN SPECIFIC, HELPER T CELL LINES BY TRANSFORMATION WITH THE RADIATION LEUKEMIA VIRUS (RADLV).

Yefenof E, Azar Y, Eidelsztein P, Ben-Sasson SZ
Lautenberg Center General and Tumor Immunology, Hebrew Univ-Hadassah Medical Sch., P.O.B 1172, Jerusalem, Israel
J Immunol; 128(2):625-628 1982

Antigen-specific immune T lymphocytes of male C57BL/6 mice were enriched in vitro on monolayers of antigen-pulsed syngeneic macrophages. The cells were treated in vitro with RadLV and inoculated intrathymically into irradiated female C56BL/6 animals. Thymomas arising in the inoculated recipients were characterized as donor- (male) type according to their karyotype. In vivo and in vitro cell lines were established from the primary lymphomas, two of which (designated ROT/6.1 and ROT/6.2) were capable of providing antigen- (carrier) specific help in normal or preimmunized mice. None of the lymphomas could induce antigen-specific DTH reaction. Five months after their establishment, ROT/6.2 alone retained its carrier specificity. ROT/6.2 consisted mainly of Lyt-1+ cells, whereas the ROT/6.1 population was more heterogeneous and contained Lyt-1+, Lyt-2+, and Lyt-3+ cells. The carrier specificity of the latter may have been lost due to selection against the specific helper cells during prolonged passages. (Author abstract) (18 Refs)

40. DIFFERENT T-CELL SUBTYPES ARE ASSOCIATED WITH PATHOLOGICALLY DISTINCT FORMS OF MOLONEY LEUKEMIA VIRUS (M-MULV)-INDUCED LYMPHOMA.

Asjo B, Skoog L, Fenyo EM, Klein G
Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm, Sweden
Int J Cancer; 29(2):163-167 1982

The T-cell enzyme markers, terminal deoxy-nucleotidyl transferase (TdT) and 20 alpha hydroxysteroid dehydrogenase (20 alpha SDH), were used to classify lymphomas induced by the Moloney leukemia virus (M-MuLV). Different subtypes of T cells were shown to be involved in different types of lymphoma. Thymomas were TdT-positive and grew as sc solid tumors at the site of inoculation. Spleen cells from mice with generalized lymphoma were of two types. In the majority of cases the lymphomas consisted of 20 alpha SDH-positive cells that homed to spleen and lymph nodes upon transplantation. In a few cases the cells of enlarged spleens were TdT-positive and, like the TdT-positive thymomas, could be transplanted as sc tumors. Thus, TdT-positive and 20 alpha SDH-positive T-cell lymphomas can be distinguished by their homing properties. Preleukemic thymus cells from M-MuLV inoculated mice can, after transfer to 400-R irradiated syngeneic hosts, induce new lymphomas by virus release or grow in an autonomous fashion in the recipients. Whether of donor or recipient type, these lymphomas are TdT-positive. In contrast, preleukemic bone marrow cells give lymphomas of donor type which are as heterogeneous for T-cell enzymes as are lymphomas induced by neonatal inoculation of M-MuLV. (Author abstract) (14 Refs)

41. DETECTION OF TYPE-SPECIFIC ANTIGENIC DETERMINANTS OF MURINE MAMMARY TUMOR VIRUSES WITH CELL-MEDIATED IMMUNE ASSAYS.

Lopez DM, Sigel MM, Schlom J
Univ. Miami, Miami, FL, 33101
Proc Soc Exp Biol Med; 169(1):144-148 1982

Cell-mediated immune assays were used to detect type differences among mouse mammary tumor viruses (MMTV) obtained from various mouse strains. The diversity of MMTVs found and their recognition by the lymphoid cells may explain variations in mouse mammary tumor development and differences in their metastatic potential. (23 Refs)

42. RESISTANCE TO MOLONEY MURINE SARCOMA VIRUS (M-MUSV) TUMOR INDUCTION IS ASSOCIATED WITH NATURAL ANTIBODY PRODUCTION TO 'ENDOGENOUS' MOLONEY LEUKEMIA VIRUS (M-MULV) IN BALB/MO MICE.

D'Andrea E, De Rossi A, Chieco-Bianchi L
Laboratorio di Oncologia, Istituto di Anatomia Patologica, Via Gabelli 61, 35100, Padova, Italia
Tumori; 67(6):511-520 1981

BALB/Mo mice are characterized by early expression of 'endogenized' M-MuLV and are resistant to M-MuSV tumor induction. Furthermore, compared to normal BALB/c mice, sera from BALB/Mo mice exhibit a significant reactivity which is specific for M-MuLV when tested in a 125I-labeled Staphylococcus protein A binding assay. The possible significance of this reactivity in conferring tumor resistance is explored. (Author abstract) (54 Refs)

43. SPECIFICITY OF TUMOR CELL STIMULATION OF DNA INHIBITORY CYTOKINE PRODUCTION IN VITRO.

Kieler J, Houssini ME
Fibiger Lab., Ndr. Frihavnsgade 70, DK-2100 Copenhagen, Denmark
Anticancer Res; 1(4):235-241 1981

Spleen cell stimulation by ST/a lung fibroblasts which have undergone 'spontaneous' malignant alteration in vitro and the cellular subpopulation involved were studied. ST/a splenocytes and peritoneal macrophages sensitized to tumorigenic, isoimmunizing R+ ST-L cells in vivo produced a DNA inhibitory supernatant in vitro when co-cultured with R+ ST-L cells. Except for primary cultures of adult ST/a lung fibroblasts, all cells had a stimulatory effect on presensitized anti-R+ ST-L1 splenocytes relative to non-sensitized splenocytes. During the first passages the stimulatory effect of non-tumorigenic stimulator cells was significatnly lower than that of R+ ST-L1 cells, but in the 13th passage the difference disappeared. By studying cross-reactions with various uninfected and murine leukemia virus infected cells, evidence was obtained for gp 70 specificity of the stimulation. T-cell depletion and whole body irradiation caused a moderate reduction of the DNA inhibitory effect of the splenocyte culture supernatant. Macrophage depletion by silicate caused an almost complete abolition of DNA inhibitory cytokine production, which could not be restored by the addition of supplementary non-sensitized spleen cells. (25 Refs)

44. TUFTSIN, A NATURAL ACTIVATOR OF PHAGOCYTIC FUNCTIONS INCLUDING TUMORICIDAL ACTIVITY.

Najjar VA, Konopinska D, Chaudhuri MK, Schmidt DE, Linehan L
Div. Protein Chemistry, Tufts Univ. Sch. Medicine, Boston, MA, 02111
Mol Cell Biochem; 41:3-12 1981

Some of the properties of the tetrapeptide tuftsin, Thr-Lys-Pro-Arg, are discussed. We describe three phases of tuftsin activation of the macrophage. Tuftsinyltuftsin, the octapeptide Thr-Lys-Pro-Agr-Thr-Lys-Pro-Arg, was synthesized with a view of minimizing the formation of Lys-Pro-Arg, from tuftsin by tissue aminopeptidases. The tripeptide is a tuftsin inhibitor. The octapeptide proved to be quite effective in prolonging the life of syngeneic mice injected with L1210 leukemia cells. Its effect in our laboratory, was considerably better than we could obtain with tuftsin. A simple method for purif ying tuftsin by high performancee liquid chromatography is described using 0.75% trifluoroacetic acid in water. The tuftsin sequence Thr-Lys-Pro-Arg is present in P12 protein of Rausher murine leukemia virus. A close analog Thr-Arg-Pro-Lys appears in yet another virus protein the hemagglutinin of influenza virus. A second close analog Thr-Arg-Pro-Arg forms the penultimate carboxyterminal of a pancreatic polypeptide found in human and several animals. (Author abstract) (44 Refs)

45. ISOLATION OF AN ANTIGEN FOR DIAGNOSIS OF ENZOOTIC CATTLE LEUKEMIA USING AGAR GEL IMMUNODIFFUSION TECHNIC.

Mateva V
Central Res. Veterinary Inst., Sofia, Bulgaria
Vet Med Nauki; 18(4):45-46 1981

A method of isolation of cattle leukemia virus antigen is described. The virus was isolated from the culture medium or from the cells of fetal lamb kidney infected with cattle leukemia virus. The antigen formed a precipitation band with the leukemic sera. Activity and specificity of precipitation band did not differ from that produced by glucoprotein antigens. The antigen was effectively used for the diagnosis of enzootic cattle leukemia. (no Refs) (In BUL)

46. INDUCTION OF SPECIFIC CELL-MEDIATED CYTOTOXICITY IN VITRO BY MEANS OF RNA ISOLATED FROM ALLOGRAFTED MICE.

Holan V, Lipoldova M, Zadrazil S, Hasek M
Inst. Molecular Genetics, Czechoslovak Acad. Sciences, 163 37 Praha, Czechoslovakia
Folia Biol (Praha); 27(6):422-426 1981

Immune RNA was prepared by sensitization of B10.A mice with allogeneic skin grafts from C57BL/10Sn mice and extraction from spleens and lymph nodes in cold phenol-chloroform-isoamyl alcohol. The RNA extracts induced specific cell-mediated immunity in vitro in lymphocytes of normal B10.A mice, demonstrated by 3H-thymidine microcytoxicity assay in surviving cells of MC11 sarcoma induced in B10 mice or in cells of two Rous sarcoma virus-induced tumors in Wistar rats or DBA mice. The RNA immunospecific cytotoxicity persisted after deoxyribonuclease and pronase treatment but not after ribonuclease treatment, indicating that RNA activity is involved in the induction process. (16 Refs)

OTHER RELATED STUDIES

47. NEW ANTITUMOR ANTIBIOTIC DC-14.

Shimizu K, Ohkubo S, Morimoto M, Tomita F
(c/o Tomita) Tokyo Res. Lab., Kyowa Hakko Kogyo Co. Ltd., Machida, Tokyo, Japan
J Antibiot (Tokyo); 35(1):87-89 1982

An actinomycete strain DO-14 (Streptomyces olivaceus) isolated from soil is shown to produce an anthraquinone antibiotic (DC-14) of molecular formula C43H50N2O13. DC-14 inhibited the growth of gram-positive and weakly gram-negative bacteria, and was active against murine sarcoma virus 180 in vivo at doses of 1.5-6.0 mg/kg. Acute toxicity (LD50) of DC-14 ip in mice was about 8 mg/kg. (7 Refs)

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VIRUS ISOLATION AND CHARACTERIZATION

1. CHARACTERIZATION OF THE RIBONUCLEIC ACID OF A TYPE D RETROVIRUS (PMFV) ISOLATED FROM A PERMANENT HUMAN CELL LINE.

Mothes E
Zentralinstitut fur Krebsforschung, Lindenberger Weg, DDR-1115 Berlin-Buch, E. Germany

Arch Geschwulstforsch; 52(3):191-197 1982

Similarities in size, subunit structure, and the presence of associated RNA of the major RNA species of permanent human fibroblasts virus (PMFV), Mason-Pfizer monkey virus (MPMV), and other retroviruses were studied. The virus was propagated in suspension culture of human rhabdomyosarcoma A204 cells. PMFV 3H-RNA was extracted from purified virus (peak fraction 1.14-1.18 g/ml) by the phenol-phase method. Comparison of the profiles showed that PMFV contains high- (60-70 Svedberg units; S) and low-mol wt (approx 7 S) components. RNA was isolated with the same method from the 1.20-1.23 g/ml peak fraction (virus core). A high mol wt species (60-70 S) was observed. Treatment with heat (65 C) resulted in

HE 20. 3173/2:

a decrease of the sedimentation coefficient to approx 30 S. Best results were obtained with RNA from fresh virus isolated from cell sediments. Chromatographic profiles obtained with 60-70 S PMFV 3H-RNA and with 30 S PMFV 3H-RNA from whole virions of virus core are shown. Radioactivity bound to the column eluted mainly at 30-45 C. This corresponded to polyadenylic acid (poly A) regions of 80-300 adenylate residues. The presence and length of the poly A stretch of PMFV RNA, the size of native 60-70 S PMFV RNA and its dissociation by heat to subunit structures of approx 30 S showed the similarity to MPMV RNA. (14 Refs)

2. VIRUS CLONED FROM THE RAUSCHER VIRUS COMPLEX INDUCES ERYTHROBLASTOSIS AND THYMIC LYMPHOMA.

Vogt M

Tumor Virology Lab., Salk Inst., Post Office Box 85800, San Diego, CA, 92138

Virology; 118(1):225-228 1982

The pathogenicity of two ecotropic viruses cloned from a Rauscher virus complex (RV), that had been passaged in the mouse, has been studied. One of the viruses, R-MuLV, gives rise to syncytia in the XC test (XC-positive), the other, R-XC- virus, does not (XC-negative). Both cloned viruses induce erythroblastosis and thymic lymphoma after inoculation into newborn NIH Swiss mice. Another clonal isolate of R-MuLV, from a stock which has been propagated in tissue culture, similarly induces both diseases when injected into newborn NIH Swiss mice. All R-MuLV and R-XC- induced splenic and thymic tumors produced, in addition to the injected virus, mink cell focus-inducing virus. This is consistent with the idea that MCF viruses are the actual (proximal) viruses causing the proliferative processes in the hematopoietic cells which lead to the different diseases. The finding that an R-MCF virus, which in most cases induces erythroblastosis, can also induce thymic lymphoma at a low frequency suggests that both diseases could be induced by the same MCF virus. (Author abstract) (18 Refs)

3. CHARACTERIZATION OF A HIGHLY ONCOGENIC MURINE LEUKEMIA VIRUS FROM WILD MICE.

Rasheed S, Pal BK, Gardner MB

Dept. Pathology, Univ. Southern California Sch. Medicine, 1840 N. Soto St., Los Angeles, CA, 90032

Int J Cancer; 29(3):345-350 1982

We have isolated a highly lymphomagenic wild mouse virus by passage of a weakly oncogenic amphotropic murine leukemia virus (MuLV-A) in NIH Swiss mice. This virus is similar in host range, interference and neutralization properties to that of the inoculated amphotropic virus but is distinct from it biochemically and causes lymphomas in 90-100% of mice within 1-2 mo. Our results indicate that this highly oncogenic virus is a recombinant of wild mouse MuLV-A and sequences related to env gene region of the endogenous xenotropic virus of NIH Swiss mice. (Author abstract) (45 Refs)

4. BIOPHYSICAL AND BIOLOGICAL CHARACTERISTICS OF A MURINE LEUKEMIA RETROVIRUS.

Ruggiero R, Carrizo D, Correa J, Pasqualini CD

Departamento de Leucemia Experimental, Instituto de Investigaciones, Hematologicas Academia Nacional de Medicina, Buenos Aires, Argentina

Medicina (B Aires); 41(Suppl):207-214 1981

Constitution of murine leukemia retrovirus was investigated. Female BALB mice 1.5-2 mo old weighing 18-20 g were inoculated with PLLV-T2 virus which induced leukemia. Acellular extracts were prepared from leukemic spleens. Filtration, ultracentrifugation, bioassay, and in vivo titration were performed and sedimentation rate were calculated. Based on the obtained data it was concluded that PLLV-T2 virus is a Type C retrovirus. (16 Refs) (In SPA)

5. LYMPHATIC LEUKEMIA AND RETRIEVAL OF DEFECTIVE FRIEND VIRUS IN ATHYMIC NUDE RATS.

Fieldsteel AH, Colston MJ, Dawson PJ

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Proc Soc Exp Biol Med; 169(3):316-319 1982

Inoculation of Friend virus (FV) into newborn athymic rats, followed by infection with lymphatic leukemia virus (LLV) resulted in development of leukemia in two rats, while the other two were aleukemic when the experiment was terminated after 135 days. Following injection of LLV into newborn athymic mice, viremia was detected in 20 days with subsequent death in approx 100 days. All seven young adult BALB/c mice infected with the same preparation of FV developed histologically confirmed Friend disease. Athymic newborn rats inoculated with LLV were later xenografted with cells from virus-free, FV-induced tumor grown in vitro. Cell free extracts of the tumors that developed induced typical Friend disease in newborn mice. Because the rat apparently lacks target cells for FV replication, the entire output of virus must have originated in the tumor itself, which is in marked contrast to findings of earlier experiments in BALB/c mice. (10 Refs)

6. DETECTION OF VSV(MULV) PSEUDOTYPES BY AN IMMUNOBIOCHEMICAL TECHNIQUE.

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Virology; 117(2):522-529 1982

Vesicular stomatitis virus (murine leukemia virus) (VSV(MuLV)) pseudotypes containing a [3H]uridine-labeled VSV RNA genome and MuLV envelope glycoproteins (gp70) were produced by phenotypic mixing of the two viruses. In order to better detect such pseudotypes, an immunobiochemical (IB) technique was developed. [3H]Uridine-labeled virus progeny of the dual virus infection was immunoprecipit ated by monospecific MuLV gp70 antibodies complexed with fixed Staphylococcus aureus. The immunoprecipitated 3H-labeled genomic RNA was identified as that of VSV by its sedimentation coefficient, by the lack of polyadenylate, and by molecular hybridization with complementary VSV RNA. By the IB technique, approx 11% of the progeny of the dual virus infection were found to be VSV(MuLV). By neutralization and other biological assays, however, only 0.1% of the progeny were found to be VSV(MuLV) pseudotypes. Apparently, the IB technique is capable of detecting VSV pseudotypes encapsidated with only a few molecules of MuLV gp70. The IB technique, therefore, offers a quantitative and molecular technique for the detection of VSV(MuLV) pseudotypes and can be modified to detect other viral pseudotypes when other assays are lacking. In spite of its sensitivity, however, the IB technique did not detect the formation of MuLV (VSV) pseudovirions among the virus progeny of the dual virus infection. These results confirmed a similar observation made previously using immunoelectron microscopy. (Author abstract) (38 Refs)

7. SEARCH FOR RETROVIRUS EXPRESSION IN MEN - FAILURE TO DEMONSTRATE RETROVIRUS-SPECIFIC ANTIGENS IN NORMAL AND MALIGNANT TISSUE.

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Arch Geschwulstforsch; 52(3):169-173 1982

Immunological experiments using the Sepharose bead immunofluorescence assay to demonstrate retrovirus antigens in different human tissues are presented. With some of the extracts (in particular from placentas and leukemic tissues) slightly positive reactions were observed, especially in the interspecies-specific type C virus assay. An unequivocally positive result could not be obtained in any case. With some samples, the test was negative when repeated, with others the values were just at the significance border and turned out to be insignificant when the competition by uninfected cellular extracts was taken as a reference. Results indicated that a virus specificity was nonexistent. (17 Refs)

VIRUS ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

8. INDUCTION OF FIBROSARCOMA BY RAT SARCOMA VIRUS.

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Virology; 118(1):219-224 1982

The rat sarcoma virus (RaSV) causes rapid transformation of rat embryo fibroblasts in vitro and induces a 29,000-dalton protein (pp29) in the transformed cells. Several strains of newborn rats were inoculated with RaSV with its natural helper rat leukemia virus (RaLV) or RaSV pseudotypes of replication competent murine leukemia virus or baboon endogenous virus. Approx 2-3% of susceptible rats developed fibrosarcomas in 12-20 wk. However, none showed any immune response or viremia over a 10-mo follow-up period. Further, we isolated RaSV from the in vivo induced tumors that transformed rat cells in vitro. Both the tumor and in vitro transformed cells exhibited the same gene product (pp29) as described earlier. (Author abstract) (17 Refs)

9. PROTEINS ANTIGENICALLY RELATED TO THE HUMAN ERYTHROCYTE GLUCOSE TRANSPORTER IN NORMAL AND ROUS SARCOMA VIRUS-TRANSFORMED CHICKEN EMBRYO FIBROBLASTS.

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Proc Natl Acad Sci USA; 79(5):1540-1544 1982

Antibody raised against the purified human erythrocyte glucose transporter specifically precipitated four proteins from normal and Rous sarcoma virus-transformed chicken embryo cells: a major protein of Mr 41,000 and minor proteins of Mr 68,000, 73,000, and 82,000. The Mr 41,000 and 82,000 proteins were found only in a membrane fraction, not in the soluble fraction, and displayed a heterogeneous mobility on NaDodSO4/polyacrylamide gel electrophoresis, suggesting glycosylation. The Mr 41,000 and 82,000 proteins were increased in amount after malignant transformation in direct proportion to the increase in hexose transport rate, and the increase was dependent on the expression of the src gene product, as revealed with a temperature-conditional src mutant. We suggest that the Mr 41,000 and 82,000 proteins are the glucose transporter of chicken embryo fibroblasts, or a component of the glucose transporter. These experiments provide direct evidence that malignant transformation increases the rate of glucose transport by increasing the number of transporters in the membrane. (Author abstract) (27 Refs)

10. AN IGM-PRODUCING B LYMPHOBLASTOID CELL LINE ESTABLISHED FROM LYMPHOMAS INDUCED BY A NON-DEFECTIVE RETICULOENDOTHELIOSIS VIRUS.

Nazerian K, Witter RL, Crittenden LB, Noori-Dalloii MR, Kung HJ
Regional Poultry Res. Lab., U.S. Dept. Agriculture, 3606, East Mount Hope Road, East Lansing, MI, 48823
J Gen Virol; 58(part2):351-360 1982

Chick syncytial virus (CSV), a strain of avian reticuloendotheliosis virus (REV) causes lymphoid tumors in chickens after a prolonged incubation period. A number of CSV-induced tumors were examined for cell surface antigen and were found to be of the B cell type and to produce immunoglobulin. Attempts were made to grow in vitro cell lines from CSV-induced tumors and a lymphoblastoid cell line was established from a liver tumor of a chicken that was inoculated with CSV via the yolk sac in embryo. The donor chicken was viremic at the time the tumor was removed. The cell line is designated RECC-RP13, it produces non-defective REV, is a B cell type and it produces IgM. It is free from infection with endogenous and exogenous avi an leukosis virus (ALV) and has an increased number of chromosomes. Sequences specific to REV were detected in at least four sites in cellular DNA from RECC-RP13. Sequences specific to ALV DNA, beyond that normally found in 15I5 x 71 cells, were not found in DNA from this cell line. (Author abstract) (31 Refs)

11. SELECTIVE EFFECT OF FELINE LEUKAEMIA VIRUS ON EARLY ERYTHROID PRECURSORS.

Onions D, Jarrett O, Testa N, Frassoni F, Toth S
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Nature; 296(5853):156-158 1982

In a survey of feline leukemia virus (FeLV) subgroups in naturally infected cats, FeLV-C was not observed in 98 clinically normal cats but was found in 9/32 anemic cats. Subgroup C viruses from three of these anemic cats were biologically cloned and used to infect neonatal kittens. Each isolate produced a pure red cell hypoplasia (RCH), the pathology of which resembled that previously described for FeLV-C/Sarma. To determine the effect of subgroup C viruses on hematopoietic precursor cells, 3.5 x 10(5) focus-inducing units of FeLV-C/Sarma were inoculated ip within 24 hr of birth into specific pathogen-free, randomly bred cats. Control and infected cats were bled weekly to determine their blood constituents and virus status. FeLV-C/Sarma infected cats showed a rapid depletion of early erythroid precursors (burst-forming units-erythroid; BFU-E) while the proportion of the myeloid precursor (granulocyte-macrophage colony-forming cells; GM-CFC) in the bone marrow remained normal. While the mechanism of FeLV-C-induced depletion of BFU-E is unknown, any hypothesis to explain the above findings must account for the remarkable selective effect of FeLV-C in producing RCH with normal levels of GM-CFC and circulating leukocytes. (25 Refs)

12. FELINE LEUKEMIA VIRUS AND HEPATITIS B VIRUS: A COMPARISON OF LATE MANIFESTATIONS.

Francis DP, Essex M, Maynard JE
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Prog Med Virol; 27:127-132 1981

Similarities and differences between feline leukemia virus (FeLV) and hepatitis B virus (HBV) are reviewed, and estimates of outcomes of HBV infection are made in a manner similar to that used with FeLV from infection-rate and mortality statistics. Cancer is probably a rare manifestation of HBV infection in the United States (0.4% of infections), whereas deaths from cirrhosis are a much more common outcome (1.8%). HBV fits a pattern expected for a naturally-occurring oncogenic virus, and treatment and research should be geared to such a hypothesis. (15 Refs)

13. FACTORS DETERMINING THE SUSCEPTIBILITY OF NIH SWISS MICE TO ERYTHROLEUKEMIA INDUCED BY FRIEND MURINE LEUKEMIA VIRUS.

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Virology; 117(2):357-365 1982

Helper-independent virus from a molecularly cloned stock of Friend murine leukemia virus (F-MuLV) induces an erythroproliferative disease characterized by splenomegaly and severe anemia in newborn mice of certain susceptible strains, such as NIH Swiss. With age, NIH Swiss mice become resistant to this F-MuLV-induced erythroleukemia. Resistance is not correlated with the replication of the input Friend MuLV but is correlated with the replication of Friend MCF viruses in the spleens of infected mice. Treatment of adult NIH Swiss mice with x-irradiation, phenylhydrazine, or silica before injection of F-MuLV increases the replication of MCF viruses in the spleens of these mice and renders them significantly more susceptible to erythroleukemia. In contrast to mice infected with F-MuLV as newborns or as x-irradiated adults, untreated 6-wk-old NIH Swiss mice develop a good humoral immune response to MCF gp70. These results suggest that the resistance of adult NIH Swiss mice to erythroleukemia induced by F-MuLV is due to the lack of replication of Friend MCF viruses in these mice because of (1) a good immune response to the virus, (2) the lack of a suitable number of susceptible target cells, or (3) both. (Author abstract) (27 Refs)

14. HEMATOPOIETIC STEM CELLS IN FRIEND MURINE LEUKEMIA VIRUS INFECTED MICE UNDERGOING CHEMOTHERAPY: FAILURE TO ERADICATE EP-INDEPENDENT ERYTHROPOIESIS BY BCNU.

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Exp Hematol; 10(2):151-160 1982

DBA/2 mice, 12 days after infection with the polycythemia-inducing Friend virus (F-MuLV-P), were treated with a single dose of carmustine (BCNU). The effect of 35 mg/kg and lower doses on the different stem cell pools (CFUS, CFUC, CFUE) and the F-MuLV-P specific ICPC (infectious centers producing cells) and Ep-independent CFUE was studied in detail. The depression of CFUs and CFUC was comparable in normal and F-MuLV-P infected mice. The CFUE population of virus infected mice, which had been completely Ep independent before treatment, showed only some normal Ep dependent colony growth thereafter. This finding was in contrast to the effect of multiple doses of hydroxyurea, studied previously, which had given the same quantitative depression of CFUS and CFUC. Possible reasons for this failure are discussed; they may be the more proliferation independent mode of action of BCNU and the delayed hemopoietic regeneration. (Author abstract) (19 Refs)

15. MIXED INFECTION OF BALB/C MICE WITH RAUSCHER LEUKEMIA VIRUS AND L FORMS OF LISTERIA.

Kotliarova GA, Biriulina TI, Snegireva AE, Kokorin IN, Konstantinova ND, Prozorovskii SV, Shevliagin VIa, Klitsunova NV
N. F. Gamalea Inst. Epidemiology and Microbiology, Moscow, USSR
Eksp Onkol; 4(1):21-25 1982

Characteristic features of mixed infection with Rauscher's leukemia virus (RLV) and L forms of listeria (LL) were studied in BALB/c mice. The 2-mo-old mice were inoculated ip with the mixture of RLV and LL (Group I), with RLV alone (Group II), or with LL alone (Group III). By day 60 after inoculation, 87% of mice in Group I died of leukemia, compared with 36% in Group II. All mice in Group III were free of leukemia. Majority of mice in Group I died on days 30-40 after inoculation, while majority of mice in Group II died on days 40-50 after the inoculation. All mice infected with RLV and LL showed marked pathological changes in the spleen: severe erythroblastosis with massive necrotic and hemorrhagic foci were observed on days 42-49 after mixed infection. Mice infected with RLV alone showed hyperplasia of the lymphoid tissue of the spleen and foci of the erythroid hematopoiesis. Mice infected with LL alone had only slight changes in the spleen. It was suggested that stimulation of RLV is associated with immunosuppressive effect of LL. (9 Refs) (In RUS)

16. PHOSPHORYLATION OF VINCULIN BY PP60SRC. WHAT MIGHT IT MEAN?

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Cell; 28(3):437-438 1982

Alterations in tyrosine kinase-specific vinculin following infection with Rous sarcoma virus pp60src are described. Vinculin is concentrated at sites of actin-membrane interaction and cell-substratum contact. Pp60src, the transforming protein of Rous sarcoma virus, is concentrated in the same regions. Changes in vinculin, alpha-actinin, and microfilament bundles following transformation are described. (no Refs)

17. PERICELLULAR MATRIX AND CELL SURFACE GLYCOPROTEINS OF VIRUS-TRANSFORMED MOUSE EPITHELIAL CELLS.

Keski-Oja J, Gahmberg CG, Alitalo K
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Cancer Res; 42(3):1147-1153 1982

Mouse embryo Mus musculus castaneous epithelial cells, transformed with Moloney murine sarcoma virus (MSV) or with ecotropic murine leukemia virus (MuLV), were analyzed for production of pericellular matrix glycoproteins. The nontransformed, MSV-transformed, and MuLV-transformed cells produced fibronectin, laminin, Type I collagen, and small amounts of Type III collagen when studied by immunofluorescence using specific antibodies. The virus-transformed epithelial cells produced enhanced amounts of fibronectin into their growth media. Nontransformed M musculus castaneous epithelial cells mainly produced Type I collagen, as shown by metabolic labeling and polypeptide analysis. A significant increase in the glycoprotein production was seen by the MuLV-transformed cells, whereas small changes in the collagen production were apparent after MSV transformation. MuLV-transformed cells produced increased amounts of Type I collagen and also some collagenous polypeptides that comigrated with procollagen Type IV chains. The ratio of the procollagen Type I chains deposited in the matrix was altered in transformed cells. Radioactive surface labeling of the cells revealed changes of the high-mol-wt glycoproteins in both the MSV-and the MuLV-transformed cells. Unlike virus-transformed fibroblastic cells, these transformed epithelial cells deposited and retained connective tissue glycoproteins in their pericellular matrices. The results indicate that viral transformation modulates the pericellular matrix and surface glycoproteins of cultured mouse epithelial cells. The ability of virus-transformed epithelial cells to deposit pericellular matrices is a major difference between them and virus-transformed fibroblastic cells. (Author abstract) (46 Refs)

18. RETINOIC ACID INDUCES ANCHORAGE- AND DENSITY-DEPENDENT GROWTH WITHOUT RESTORING NORMAL CYTOSKELETON, EGF BINDING, FIBRONECTIN CONTENT AND ODC ACTIVITY IN A RETROVIRUS-TRANSFORMED MOUSE CELL LINE.

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Exp Cell Res; 138(1):95-107 1982

We studied the effects of retinoic acid (RA), a known tumor inhibitor, on a group of transformation-related properties expressed by a Kirsten sarcoma virus (Ki-MSV)-transformed BALB/c 3T3 (clone A31) cell line (KA31). The aim was to determine whether any one or a group of such transformation-specific changes, exhibited by this cell line, is an absolute prerequisite for its acquisition of the neoplastic state. Our study shows that RA treatment restores two important parameters of normalcy in KA31 cells: density-dependent growth inhibition, and anchorage-dependent growth. Retinoic acid also induces cell-to-substratum adhesiveness in a significant proportion of the treated KA31 cell population. However, four other markers of transformation - loss of microfilaments, lack of surface fibronectin, reduced epidermal growth factor (EGF) binding, and increased ornithine decarboxylase activity - remain unaltered by RA treatment. These transformation-specific changes, therefore, are dissociable from loss of anchorage- and density-dependent growth. It is suggested that RA may intervene in transforming protein kinase-induced cell surface changes that are involved in cellular malignancy and the loss of growth control in KA31 cells. (Author abstract) (57 Refs)

19. LESS MEMBRANE-ASSOCIATED ACTIN IN TRANSFORMED VERSUS NORMAL RAT KIDNEY CELLS.

Rubin RW, Suchard SJ, Ozores JN
Dept. Anatomy, Univ. Miami Sch. Medicine, Miami, FL, 33101
Cell Biol Int Rep; 6(2):177-187 1982

The amount of membrane-associated (MA) actin was compared in normal rat kidney (NRK) cells and their Kirsten viral transformants (442 cells). Entrapment of non-specific proteins and/or chemically induced alterations of plasma membrane incurred during isolation were overcome by employing an isolation procedure which does not require gradient purification, sonication, or the use of chemical membrane stabilizers or detergents. Plasma membranes were isolated by adhering NRK and 442 cells to a poly-L-lysine treated surface, and lysing them with hypotonic buffer. Results showed that MA actin to total MA protein ratio is significantly greater for NRK than for 442 cells. (24 Refs)

20. CONTACT RELATIONSHIPS BETWEEN CHICK EMBRYO CELLS GROWING IN MONOLAYER CULTURE AFTER INFECTION WITH ROUS SARCOMA VIRUS.

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Dept. Zoology, Univ. Coll. London, Gower St., London WC1E 6BT, England
Exp Cell Res; 138(1):147-157 1982

An electron microscopic examination was made of cell contacts and associated microfilament arrays in subconfluent cultures of chick embryo fibroblasts (CEF) and chick embryo retinal pigmented epithelium cells (RPE) transformed by strains of Rous sarcoma virus (RSV) imparting a rounded (Morph r) or fusiform (Morph f) transformed morphology. A few cell substrate contact specializations were found in Morph r-transformed CEF and RPE cells. These resembled cell/substrate plaques of uninfected fibroblasts, but lacked associated microfilament tracts. In contrast Morph f-transformed CEF and RPE resembled untransformed fibroblasts having well developed cell/substrate and cell/cell contact specializations with extensive associated microfilament arrays. Morph r- and Morph f-transformed RPE cells had lost the junctional complex typical of untransformed RPE cultures and additionally no melanosomes were found. SEM and TEM demonstrated differences in adhesive properties of CEF and RPE cell surfaces, few virions adhering to the free cell surface of RPE cells but being found in clumps and singly on CEF cells. (Author abstract) (36 Refs)

21. THE RESPONSE OF CHICKEN EMBRYO DERMAL FIBROBLASTS TO CYTOCHALASIN B IS ALTERED BY ROUS SARCOMA VIRUS-INDUCED CELL TRANSFORMATION.

Menko AS, Croop J, Toyama Y, Holtzer H, Boettiger D
Dept. Genetics and Cell Biology, Univ. Minnesota, St. Paul, MN, 55108
Mol Cell Biol; 2(3):320-330 1982

Immunofluorescence and electron microscopy were used to study the effects of cytochalasin B on intermediate filaments and cellular morphology of chick embryo dermal fibroblasts infected with a Rous sarcoma virus mutant (tsLA24A) which is temperature-sensitive for transformation. Effects of cycloheximide and colcemid on cell morphology at both permissive and nonpermissive temperatures were also studied. Results suggest that intermediate filaments may play a role in cell morphology and that this function is affected by cell transformation. (48 Refs)

22. RECEPTOR-ASSOCIATED CHANGES OF THE CATECHOLAMINE-SENSITIVE ADENYLATE CYCLASE IN GLIOMA CELLS DOUBLY TRANSFORMED WITH MOLONEY SARCOMA VIRUS.

Higashida H, Miki N, Tanaka T, Kato K, Nakano T, Nagatsu T, Kano-Tanaka K
Cancer Res. Inst., Kanazawa Univ., Kanazawa 920, Japan
J Cell Physiol; 110(2):107-113 1982

Activity of adenylate cyclase (AC) and the receptor binding assay of 3H-dihydroalprenolol (DHA) for the beta-adrenergic receptor of C6 glioma cells doubly transformed with Moloney sarcoma virus (C6V-1 cells) were carried out as a model system for viral modification of the plasma membrane and compared with those of C6 cells. Intracellular cyclic AMP levels and intracellular phosphodiesterase, mitochondrial monoamine oxidase, and cytosomal enolase activities were measured in both cell lines. C6V-1 cells differed from C6 cells morphologically. C6V-1 cells were composed of large numbers of both round and fusiform cells, whereas C6 cells contained predominantly fusiform cells. C6V-1 cells grew faster than C6 cells with mean doubling times of 17 and 22 hr, respectively. The basal activity of AC was always lower in C6V-1 cells than in C6. Effects of Mg++, prostaglandin E1, isoproterenol, and norepinephrine on AC activity were determined in both cell lines. Fewer DHA binding sites were observed in C6V-1 cells than in C6 cells. Intracellular cyclic AMP content in C6 and C6V-1 cells was 10.1 and 4.4 picomoles/mg protein, respectively. Phosphodiesterase activity in C6 cells was 3x greater than that in C6V-1 cells, with mean activities of 91 and 31 picomoles/mg protein, respectively. Both cell types showed type A mitochondrial monoamine oxidase activity in the range of approx 70-90 picomoles/min/mg protein. Enolase activity was higher in C6V-1 cells than in C6 cells, with specific activities of 1.6 and 2.3 units/mg protein, respectively. (30 Refs)

23. CORRELATION BETWEEN THE RATES OF AEROBIC GLYCOLYSIS AND GLUCOSE TRANSPORT, UNRELATED TO NEOPLASTIC TRANSFORMATION, IN A SERIES OF BALB 3T3-DERIVED CELL LINES.

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Cancer Res; 42(5):1809-1816 1982

The relationship between transformation, lactate production, and glucose transport was examined in a series of 10 cell lines consisting of subclones of BALB 3T3 A31 cells and viral and chemical transformants of either the subclones or the original A31 line. Comparisons were made over a relatively narrow range of cell densities to minimize changes in the biochemical parameter during growth. A nitroquinoline oxide (NQT-3T3-714) and a temperature-sensitive Kirsten sarcoma virus (tsKi-3T3-714) transformant of subclone 714 exhibited transformed phenotypes with respect to morphology and growth properties, but their rates of lactate production and 2-[3H]deoxy-D-glucose (deoxyglucose) uptake were similar to those of the parent cells. Inhibitors of oxidative phosphorylation increased glycolysis fold in these trans formants, showing that there was no defect in the enzymes of this pathway. At a temperature non-permissive for transformation of tsKi-3T3-714, lactate production by this line did not decrease relative to the rate of the parent cells. Another transformant, Ki-3T3-234, had a glycolytic rate which was 4 to 5x greater than that of the low lactate producers while other transformants exhibited intermediate rates, and the rate of a third nontransformed 3T3 A31 subclone, K-1-1, was comparable to the rate of Ki-3T3-234. The rates of [3H]deoxyglucose uptake by this series of cells were closely proportional to their glycolytic rates rather than to their state of transformation. Increasing glycolysis by oligomycin or dinitrophenol treatment, however, did not cause a concomitant increase in sugar uptake. Neither glycolysis nor deoxyglucose uptake in the high-lactate producer (Ki-3T3-234) was inhibited by ouabain, suggesting that Na+-K+ adenosinetriphosphatase is not a regulator of these functions in 3T3 cells. In 3T3-derived cells, it appears that the rates of glycolysis and glucose uptake may be regulated in tandem under some conditions and that neither process is an obligatory consequence of neoplastic transformation. (Author abstract) (31 Refs)

24. CELLULAR PROLIFERATION KINETICS OF THE MURINE SARCOMA INDUCED BY THE MOLONEY SARCOMA VIRUS.

Smadja-Joffe F, Le Bousse-Kerdiles MC, Klein B, Malaise EP, Jasmin C, Degiorgis V
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Cell Tissue Kinet; 15(2):169-178 1982

Cell proliferation kinetics of the sarcoma induced by Moloney virus was studied in newborn Swiss OFl mice. After in vivo injection of tritiated thymidine, followed by autoradiography, it was shown that the majority of cells were actively proliferating (labeling index; 31%, growth fraction 78%). The mean cell cycle was 16 hr and cell loss was relatively low (cell loss factor 48%). The study of tumor specific activity with time after a single [in vivo] injection of [3H]dR or [125I]UdR did not demonstrate the same degree of cell loss as that calculated by autoradiography. This result is consistent with a massive reutilization of radioactivity released by normal tissues. (Author abstract) (20 Refs)

25. MAMMARY TUMOR VIRUS DNA AS A MARKER FOR GENOTYPIC VARIANCE WITHIN HORMONE-RESPONSIVE GR MOUSE MAMMARY TUMORS.

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Cancer Res; 42(3):1154-1158 1982

Mammary tumors of GR mice acquire extra mammary tumor virus (MMTV) DNA information within their DNA during tumor growth and development. These extra MMTV genes have been used by us as gen otypic markers to investigate the heterogeneity of GR mammary tumors and their loss of hormone dependence during serial transplantation. Our studies reveal that the various subpopulations of cells within individual GR mammary tumors are characterized by differences in number and location of acquired extra MMTV DNA fragments. Losses of certain of these extra MMTV DNA fragments occur when mammary tumors become hormone independent, indicating a loss of hormone-dependent cells. The study of MMTV DNA markers also reveals that low levels of autonomous cells are already present in some hormone-dependent mammary tumors at an early stage of their development. The genotypic analysis strongly indicates that mammary tumor progression is not due to phenotypic adaptation but to clonal selection of the more aggressive sublines. (Author abstract) (20 Refs)

26. EPIDERMAL GROWTH FACTOR AND INSULIN CAUSE NORMAL CHICKEN HEART MESENCHYMAL CELLS TO PROLIFERATE LIKE THEIR ROUS SARCOMA VIRUS-INFECTED COUNTERPARTS.

Balk SD, Shiu RP, LaFleur MM, Young LL
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Proc Natl Acad Sci USA; 79(4,part1):1154-1157 1982

Normal chicken heart mesenchymal cells at low culture density are proliferatively quiescent in a physiological culture medium containing heparinized, heat-inactivated, chicken plasma at 10%. Rous sarcoma virus-infected chicken heart mesenchymal cells, on the other hand, proliferate maximally in this same medium, undergoing a 60-fold increase in cell number during 4 days of exponential growth. When normal heart mesenchymal cells are cultured for 4 days in the presence of epidermal growth factor at 1 ug/ml they undergo a 16-fold increase in number, with graded responses to lower concentrations of the factor. In the presence of insulin at 10 ug/ml, normal heart mesenchymal cells multiply by a factor of 3 over a 4-day period. The addition of epidermal growth factor (1 ug/ml) and insulin (10 ug/ml) to cultures of normal chicken heart mesenchymal cells causes these cells to proliferate at a rate comparable to that of their RSV-infected counterparts. (Author abstract) (22 Refs)

27. PERMEABILITY OF DIFFERENT EXPERIMENTAL BRAIN TUMOR MODELS TO HORSERADISH PEROXIDASE.

Groothuis DR, Fischer JM, Lapin G, Bigner DD, Vick NA
Div. Neurology, Evanston Hosp., 2650 Ridge Ave., Evanston, IL, 60201
J Neuropathol Exp Neurol; 41(2):164-185 1982

The permeability of different brain tumor models to horseradish peroxidase (HRP) was examined by determining the fraction of tumor that contained HRP after intravenous administration. The intracerebral tumor models studied were Avian Sarcoma Virus (ASV)-induced tumors and tumors from transplanted RG-2, S69-C1-5, and 9L cell lines. The av fraction of RG-2 tumors permeable to HRP was 0.95; of S69-C1- 5 tumors, 0.699; of ASV-induced tumors, 0.63; and of 9L tumors, 0.52. Except for the RG-2 tumors, there was considerable regional variation in HRP permeability, which was most marked in the ASV-induced tumors. In ASV-induced tumors, HRP permeability did not correlate with tumor histological classification, size, or anatomic location within the brain. The subcutaneous tumor models studied were RG-2-, S69-C1-5, and 9L-transplanted tumors in rats, and human glioblastoma cell lines transplanted into nude mice. All were completely permeable to HRP. These results indicate that significant differences in permeability to HRP exist among brain tumor models when the tumors are intracerebral, and that all subcutaneous tumors from transplanted glial cell lines are completely permeable to HRP. These variables must be considered in future studies of permeability in experimental brain tumors. Care must be exercised in extrapolating results about permeability from one brain tumor model to another. (Author abstract) (27 Refs)

28. COMPARATIVE ULTRASTRUCTURE OF HUMAN GLIOMAS AND EXPERIMENTAL GLIOMAS INDUCED BY ROUS SARCOMA VIRUS (RSV).

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Laboratoire de Medecine Experimentale, College de France, 11, place Marcelin-Berthelot, F 75231 Paris, France
Neurochirurgie; 27(5):251-253 1981

Conventional and electron microscopic investigation of 20 gliomas induced by intracerebral inoculation of Rous sarcoma virus revealed great similarities between canine and human tumors. The principal types of glioma studied was the astrocytoma or spongioblastoma. The astrocytes were large with very clear nuclei and obvious nucleoli which were often filamentous. The cytoplasm contained abundant fibrillar structures and Rosenthal bodies. Sometimes the surfaces of the astrocytes were drawn out into thick bundles. Numerous microglial cells were also a characteristic of this type of glioma. Except for certain structures which have been termed 'intracisternal tubular inclusions', nothing was found which provided morphological proof that the tumors were viral induced. In humans where the glioma ultrastructure is similar, the argument for possible viral etiology is not considered weakened by the absence of viral particles in the animal models. Intracisternal tubular inclusions have been found to be associated with many viral infections. The absence of signs of viral induction, the large size of the animal, and the morphological similarities of the animal and human gliomas are all considered positive factors in the development of this experimental model for studying gliomas. (3 Refs) (In FRE)

29. GLIOMAS INDUCED IN MAMMALS BY ROUS SARCOMA VIRUS.

Rabotti GF
Laboratorie de Medecine Experimentale, College de France, 11, place Marcelin-Berthelot, F 75231 Paris, France
Neurochirurgie; 27(5):247-249 1981

Meningeal tumors induced by Rous Sarcoma virus (RSV) have been produced in chickens, rabbits, cats, and dogs. Nonhuman primates have also been used, but the in vivo results following inoculation have been negative. The greatest percentage of positive results has been obtained following intracerebral inoculation in the course of the 24 hr following birth. Tumors have been induced in older animals but the number of positive cases is considerably reduced. Most induced tumors were histological mixed types, but true gliomas have been observed. Infectious doses of RSV induced tumor formation in the chicken which is the natural host of the virus. In mammals oncogenic doses had to be injected to induced tumor formation. Efforts are currently underway to fix antiviral antibodies on the surface of glioma cells in vivo in hamsters, rats, and dogs. Further studies include the in vivo fixation of immune lymphocytes. Nothing is presently known of the immune response in an animal with a primary glioma induced by RSV. (17 Refs) (In FRE)

30. THE PRINCIPAL FIELDS OF RESEARCH INTO THE PATHOGENESIS OF GLIOMAS.

Cohadon F
Laboratoire de Neurochirurgie Experimentale et Neurobiologie, Groupe Hospitalier Pellegrin, place Amelie-Raba-Leon, F 33000 Bordeaux, France
Neurochirurgie; 27(5):241-245 1981

Experimental models studying the pathogenesis of gliomas are focused on chemically or viral induced tumors in animals. The transplacental injection of ethyl-nitrosourea in rats has produced a high rate (80-100%) of cerebral tumors of mixed types in the offspring. Repeated injections of methyl-nitrosourea in the adult rat has produced more homogenous cerebral tumors (glioblastomas most often) in 60-70% of the rats. Viral induced tumors have been produced in dogs inoculated at birth with intracerebral injections of Rous sarcoma virus. Glioma promotion is considered a result of the failure of a hypothetical immune mechanism of surveillance. The absence of systemic metastases of the gliomas is an indirect but convincing proof in favor of a surveillance immune system which eliminates the malignant cells when they leave the immunological protection of the brain. This theory is further supported by the clear immunosuppression of some patients with gliomas. At the present time, there is not definite identification of initiation or promotion factors in the pathogenesis of human gliomas. (7 Refs) (In FRE)

31. IMPROVED SPATIAL AND TEMPORAL RESOLUTION IN AN APPARATUS FOR TIME-LAPSE PHASE CONTRAST CINE LIGHT MICROGRAPHY OF CELLS IN VITRO.

Vesely P, Maly M, Cumpelik J, Pluta M>, Tuma V
Inst. Molecular Genetics, Praha 6, Czechoslovakia
J Microsc; 125(1):67-76 1982

An improved apparatus for time-lapse cinematography, which combines the highest possible spatial resolution with phase contrast and an improved temporal resolution provided by flash light illumination, is described in detail. The use of this inverted microscope system is described in applications with cell surface mobility and details of ruffling activity, in studies of temperature sensitivity of cells transformed by ts mutants of Rous sarcoma virus, and for control of cell morphology in cells to be examined by scanning electron microscopy. Oil immersion objectives of widely different magnification and resolution may be changed quickly, permitting investigation of collisions between normal and neoplastic cells in vitro. (1 Ref)

32. A COMPARISON OF THE PATHOBIOLOGY AND EPIDEMIOLOGY OF CANCERS ASSOCIATED WITH VIRUSES IN HUMANS AND ANIMALS.

Essex M, Gutensohn N
Dept. Microbiology, Harvard Univ. Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115
Prog Med Virol; 27:114-126 1981

Several oncogenic viruses in animals (chicken, cat, ox, gibbon, rabbit) are discussed in terms of characteristics and epidemiological features and are compared with human malignancies most likely to be caused by a virus (leukemias, Hodgkin's disease, Burkitt's lymphoma, cervical cancer, nasopharyngeal cancer, and primary hepatocellular carcinoma). Cancers of industrialized countries tend to be associated with environmental or dietary agents, whereas those in the developing world are likely to be of viral origin, suggesting that a vaccination program would have a profound effect in developing countries. (52 Refs)

33. FELINE LEUKAEMIA VIRUS INFECTION.

Randles JL
P.O. Box 1, 4920 Kei Road, South Africa
J S Afr Vet Assoc; 52(3):259-265 1981

Feline leukemia virus (FeLV) is reviewed with emphasis on clinical aspects. Etiology, incidence, transmission, source of infection, immunity, susceptible hosts, pathogenesis, and pathology are presented. Clinical findings, diagnosis, and treatment, of malignant neoplasms and non-neoplastic diseases involving FeLV are discussed. Possible methods of control are described. (24 Refs)

34. NATURE OF CANCER.

Dulbecco R
Salk Inst., La Jolla, CA
Boll Soc Ital Biol Sper; 57(18):21-30 1981

Fight against cancer is discussed. Two approaches are considered: a pragmatic one, using any means even those that are only partially effective, and a more general type trying to elucidate cellular changes, and their mechanisms and causes. The following topics are included oncogenic viruses and genes, differences in oncogenic mechanisms of sarcoma and leukemia viruses, promotor, chemical oncogenic induction, initiation, facilitation, differences between species (man, rat, mouse), and validity of animal testing. (no Refs) (In ITA)

35. REVERSION OF CANCER CELLS.

Boiron M
Service des Maladies du Sang, Hopital Saint-Louis, Institut de Recherches d'Hematologie et d'Oncologie, 2, place du Docteur A. Fournier, 75475 Paris Cedex 10, France
Pathol Biol (Paris); 30(3):133-135 1982

Three models of cancer cell reversion are presented, and the following reversion of cells transformed in vitro by oncogenic viruses, collection of normal cells after blockage of differentiation in leukemic cells, and possible differentiation in teratocarcinomas leading to loss of malignancy. In vitro, certain DNA and RNA viruses can transform normal cells into malignant cells with modifications of growth parameters, cellular surface characteristics, cytoskeleton, and nucleotide pool; these virus-transformed cells are capable of tumorigenesis in vivo. Temperature-sensitive mutants of the viral oncogene include normal cells produced from virus-transformed cells. In another model, apparently normal revertant cells may be observed at low frequencies; in vivo, the cells rarely loose their oncogenic potential completely. Dimethylsulfoxide modifies the morphology of Friend's leukemia cells thereby releasing the inhibition that prevents the normal execution of the genetic program; normal differentiation coincides with lost of malignancy. Other leukemia models of reversion are described. Reversion of teratocarcinoma cells is discussed in relation to treatment with retinoids. (no Refs) (In FRE)

36. PROGRESS TOWARDS A UNIFIED THEORY OF THE MECHANISMS OF CARCINOGENESIS, III: CIRCUMVENTION OF PROLIFERATION CONTROLS.

Hull LA
104 Depot St., New Sharon, IA, 50207
Med Hypotheses; 8(1):85-93 1982

Examples of mechanisms of carcinogenesis by circumvention of controls over proliferation are presented. RNA tumor viruses produce kinases that are independent of cyclic AMP. These kinases transform most cells by acting on tyrosine residues in several types of proteins. Viral kinases may reduce the efficiency of the sodium pump by modifying a protein component of the pump. The reduction in efficiency may in turn cause the increased glycolysis found in many tumors. Viral kinases may also interfere with actin filaments, affecting contact inhibition of proliferation. Because viral kinases are similar to epidermal growth factor (EGF), they may circumvent EGF requirements for proliferation. Epigenetic modifications of gene expression may be produced by phosphorylation of nonhistone chromosomal proteins. Malignant melanoma cells (MMC) do not produce melanocyte contact inhibitory factor (MCIF), which inhibits growth of tumor cells. MMC produce a similar compound, but do not release this compound. Carcinogenesis may thus result from alteration of the ability of cells to release control factors. Alkylating carcinogens may act by several mechanisms, including interference with methyl transferases, alkylation of DNA, and alkylation of chromosomal proteins. The existence of many possible mechanisms for loss of control of proliferation is indicated, suggesting that no single treatment is possible for all cancers. Understanding the various mechanisms may, however lead to more effective treatments for specific cancers. (26 Refs)

VIRUS REPLICATION AND EXPRESSION

37. ADSORPTION OF ROUS SARCOMA VIRUS TO GENETICALLY SUSCEPTIBLE AND RESISTANT CHICKEN CELLS STUDIED BY LASER FLOW CYTOMETRY.

Notter MF, Leary JF, Balduzzi PC
Dept. Microbiology, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY, 14642
J Virol; 41(3):958-964 1982

Quantitative binding of Rous sarcoma virus (RSV) of different antigenic subgroups of chicken cells was examined by using a laser flow cytometer/cell sorter. RSV of subgroups A, C, and E, labeled with the fluorescent membrane probe rhodamine-18, bound 2 to 10 times more to genetically susceptible chicken embryo fibroblasts than to resistant cells, as measured by flow cytometry on a single-cell basis. This suggested that susceptible cells possess both specific and nonspecific receptors for virus adsorption, whereas resistant cells bind virus only by means of nonspecific sites. Polybrene at low concentration increased eightfold the binding of virus. Higher levels of Polybrene inhibited adsorption. Cell binding sites were saturable, and attachment of labeled virus could be partially blocked by preexposure of cells to unlabeled RSV. Virus surface glycoproteins played an important role in adsorption, since their removal with bromelain decreased binding of virus to susceptible cells. Maximal binding of RSV to both susceptible and resistant cells occurred within 10 min, although the level of binding was up to 10-fold higher for susceptible cells. Binding to all cell types showed a broad distribution. This implies that there are considerable differences in the number of virions bound per cell. (Author abstract) (29 Refs)

38. TUMOR PROMOTER-STIMULATED SYNTHESIS OF MASON-PFIZER MONKEY VIRUS.

Wunderlich V, Baumbach L, Sydow G
Central Inst. Cancer Res., Acad. Sciences German Democratic Republic, Lindenberger Weg 70/80, DDR-1115 Berlin, E. Germany
J Cancer Res Clin Oncol; 102(3):271-275 1982

The tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA) increases by severalfold the synthesis of Mason-Pfizer monkey virus (MPMV), a type D retrovirus, when the virus is growing in human embryo kidney (HEK) cells. The effect is transient and paralleled by a striking morphological alteration of the cells. The optimal TPA concentration for stimulation is 5 ng/ml. Contrary to infected HEK cells, TPA induces at similar concentrations neither stimulation of MPMV synthesis nor altered morphology in persistently MPMV-infected cells of the continuous human tumor cell line A 204. (Author abstract) (15 Refs)

39. IDUR INDUCTION OF A NEW TYPE OF RETROVIRUS-LIKE PARTICLE (EPSILON PARTICLE) IN TRANSFORMED FIBROBLASTIC MOUSE CELLS.

Lasneret J, Canivet M, Bittoun P, Peries J
Departement d'Oncologie Experimentale, U-107 INSERM, L. 0. I. CNRS, Institut de Recherches sur les Maladies du Sang, Hopital Saint-Louis, 75475 Paris Cedex 10, France
Ann Virol; 132(2):151-159 1981

Iododeoxyuridine (IdUr) induced a virus-like structure in fibroblastic BALB/c mouse cells transformed by the Kirsten strain of murine sarcoma virus (Ki-BALB cells). Confluent cultures were treated for 24 hr with 40 ug/ml IdUr and the cells were examined by electron microscopy at 24 and 48 hr post-treatment. No type C virus particles were observed in untreated control cells. IdUr-treated cells showed abundant budding and free C particles and a significant increase in the number of IA particles. A third virus-like particle was observed in treated cells. The structures were spherical with a diameter of 75-85 nanometers and were generally located in the cisternae of rough endoplasmic reticulum. The viral-like particles were observed in groups of 10 or more units and were sometimes intermixed with IA particles. Approx 5% of treated cells contained the particles. The particles were virtually identical to epsilon particles, named for the wheel-like intracisternal structures found in oocytes and early mouse embryos and resembling golden hamster R particles. (17 Refs)

40. ULTRASTRUCTURAL EXPRESSION OF INCOMPLETE VIRUS-LIKE PARTICLES IN MURINE MYELOBLASTS GROWING IN VITRO.

Karpas A, Greenberger J
Dept. Haematological Medicine, Cambridge Clinical Sch., Hills Road, Cambridge, England
Ann Virol; 132(2):295-302 1981

The expression and development of incomplete virus-like particles (VLP) within cytoplasmic inclusion bodies of murine myeloblastic leukemia cells growing in vitro, morphologically different from A-, B-, and C-type particles are discussed. Cell lines DB18 and DB15 were studied. The cell lines have been characterized biologically for the presence of granulocyte-macrophage-specific intracellular enzymes, and both synthesize myeloperoxidase and lysozyme. Electron microscope examination revealed that the cytoplasm of all the cell sections examined from both lines contained inclusion bodies (IB). The number of IB/section ranged from 3 to over 50. Electron-dense subunits appear to form circular particles with or without tail formation. Extracellular budding of C-type virus particles from the cell membrane could not be seen in any over 200 cells examined from each of the two lines. Complete C-type particles could be found in two extracellular areas of those cells examined. They were present in a restricted area together with smaller particles which are probably incomplete viruses. The very large number of cytoplasmic inclusion bodies, many of which contain VLP in different stages of their development, suggest that those IB are probably viroplasms, rather than cytoplasmic organelles. (13 Refs)

41. LACK OF RETROVIRUS GENE EXPRESSION IN TERATOCARCINOMA STEM CELLS IS LIMITED TO T HE NUCLEUS.

Gautsch JW
Dept. Immunopathology, Res. Inst., Scripps Clinic, La Jolla, CA, 92037
Somatic Cell Genet; 8(2):143-149 1982

Complementation of Moloney murine leukemia virus (MuLV) growth in undifferentiated embryonal carcinoma (EC) cells was investigated. EC-A cells were infected with M-MuLV and then fused with whole differentiated cells, cytoplasts, or karyoplasts in the presence of 50% polyethylene glycol or Sendai virus at 8-14 hr after infection. Three days later the cells were stained and the number of syncytial plaques was counted. None of the cytoplast fusions resulted in complementation of virus growth, while control fusions between infected EC and differentiated whole cells resulted in virus growth. Differentiated cell karyoplasts complemented virus growth in infected EC cells at an efficiency equal to that of whole cells. Karyoplasts from EC cells did not complement virus growth in infected EC cells. Thus, complementation of virus growth in EC/differentiated cell heterokaryons is due to the presence of a differentiated cell nucleus. These results may be due to a function required for virus growth in differentiated cell nuclei that is not expressed or is not functional in EC cells; arternatively, the EC cell nucleus could have interrupted the progression of proviral replication by an inhibition acting in cis that might prevent transcription of the integrated viral DNA or by a trans-dominant inhibition that would be limited to the nucleus but would act to prevent integration or further expression of the viral DNA. (19 Refs)

42. INTRACELLULAR LOCALIZATION OF CERTAIN MEMBRANE GLYCOPROTEINS IN MOUSE T-LYMPHOMA CELLS USING IMMUNOFERRITIN STAINING OF ULTRATHIN FROZEN SECTIONS.

Bourguignon LY, Butman BT
Dept. Anatomy, Sch. Medicine, Univ. Miami, Miami, FL, 33101
J Cell Physiol; 110(2):203-212 1982

Morphology observed with frozen thin sections of mouse T-lymphoma cells was compared with that of epon thin sections, with special emphasis on membranous organelles. The intracellular localization of several types of membrane glycoproteins in the T-lymphoma cell system was examined. No significant differences were found between epon and frozen thin sections. Immunoferritin staining on frozen thin sections was specific, reliable, and suitable for intracellular localization of various membrane glycoproteins based on studies using antibodies directed against Thy-1, a T-cell-specific membrane glycoprotein. Many of the membranous cellular structures of the T-lymphoma cells contained the concanavalin A-specific sugars, alpha-D-mannose and alpha-D-glucose. The intracellular distribution of the viral membrane protein, gp 69/71, was studied in lymphoma cells known to be productively infected with a C-type RNA virus. Gp 69/71 molecules were detected on the surface of free and budding C-type viral particles. Occasionally, gp 69/71 w as also found in discontinuous patchlike arrays along certain regions of the T-lymphoma cell surface. Viral antigens were found in terminal regions of certain flattened rough endoplasmic reticulum membranes, in a diffuse pattern at certain regions of the stacked Golgi membranes, and in clustered arrays within small vesicle-like structures either close to the plasma membrane or at an apparent point of contact between an individual vesicle and the plasma membrane. (19 Refs)

43. MICROTUBULE-DEPOLYMERIZING AGENTS INHIBIT MOLONEY MURINE LEUKAEMIA VIRUS PRODUCTION.

Satake M, Luftig RB
Dept. Microbiology and Immunology, Univ. South Carolina Sch. Medicine, Columbia, SC, 29208
J Gen Virol; 58(part2):339-349 1982

The effects of microtubule-depolymerizing agents on virion production in MJD-54 cells chronically infected with Moloney murine leukemia virus were examined. By measuring the amount of reverse transcriptase activity remaining in particles recovered from culture fluids, we found that incubation with 1 uM- or 10 uM-colchicine, vinblastine or nocodazole resulted in 30 to 40% decreases in virus production. The decrease in virus production did not seem to be due to general damage to the cells since cellular RNA and protein synthesis were only slightly, if at all, inhibited by the drug treatment (less than 10%). Furthermore, virus proteins accumulated inside drug-treated cells, viz, [35S]methionine-labeled Pr65gag showed a 1.5-fold increase over a 3 hr continuous label interval. Consistent with this accumulation of virus protein, electron microscope studies showed that inside drug-treated cells there was a 2-to 2.5-fold accumulation of virions within cytoplasmic vesicles. All of these results support the idea that cytoplasmic microtubules play a role in the production of murine leukemia virus. (Author abstract) (28 Refs)

44. FORMATION OF THE ENVELOPE OF ROUS SARCOMA VIRUS AND VESICULAR STOMATITIS VIRUS FROM LOCALIZED LIPID REGIONS IN THE PLASMA MEMBRANE.

Omann GM, Cimino J, Pessin JE, Glaser M
Dept. Biochemistry, Univ. Illinois, Urbana, IL, 61801
Biophys J; 37(1):135-136 1982

The effects of altering the host cell plasma membrane lipid composition and fluidity on the viral envelope lipid composition and fluidity were determined in chick embryo fibroblasts treated with a Rous sarcoma virus mutant (RSV-T5). Results showed differences in the lipid composition of the plasma membrane from RSV-T5 infected cells grown at 36 C or 41 C. However results of 1.6-diphenyl-1,3,5-hexatriene (DPH) anisotropies showed identical virions produced by the cells. Steady state and limiting anisotropies of DPH in the supplemented plasma membranes and vesicular stomatitis virus envelopes were similar. The virus apparently selectively incorporates host cellular phospholipids into the viral envelopes. (6 Refs)

45. DIAGNOSIS OF BOVINE LEUKOSIS VIRUS INFECTION BY SOLID PHASE RADIOIMMUNOASSAY FOR VIRUS ANTIBODY.

Zajac V, Altaner C
Cancer Res. Inst., Slovak Acad. Sciences, 812 32 Bratislava, Czechoslovakia
Neoplasma; 28(6):661-668 1981

Solid phase radioimmunoassay for detection of anti-BLV antibodies in sera of infected animals is described. Viral antigens bound to the surface of polystyrene are able to selectively adsorb the antibodies from serum. Detection of bound antibodies quantitatively was done by 125I-labeled protein A from Staphylococcus aureus. Technical details of the assay are reported. The assay could be used as a competitive one as well. Two different methods for detection of anti-BLV antibodies were compared with solid phase RIA. The solid phase RIA is highly sensitive, specific and available for large-scale examination. The assay is recommended for early diagnosis of bovine leukosis. (Author abstract) (18 Refs)

GENETICS

46. SUPPRESSION OF SPONTANEOUS LYMPHOMA BY PREVIOUSLY UNDISCOVERED DOMINANT GENES IN CROSSES OF HIGH- AND LOW-INCIDENCE MOUSE STRAINS.

Chen S, Lilly F
(c/o Lilly) Dept. Genetics, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Virology; 118(1):76-85 1982

Crosses of mice of the high-lymphoma mouse strains, AKR and C58, with mice of the low-lymphoma strains, C57L, DBA/1, and DBA/2, produce F1 generations with low and late incidences of the spontaneous disease. Backcross populations, obtained from high-lymphoma parental strain x low-lymphoma F1 matings, showed lymphoma incidences of approx 75%, indicating that the low lymphoma incidence in F1 mice of these crosses was due to the simultaneous presence of at least two independently segregating dominant genes inherited from the low-lymphoma parental strain. In none of the three crosses was lymphoma resistance linked to the Fv-1 locus, and in only one (AKR x C57L) was H-2 type a significant determinant of the disease. This finding indicates that previously undiscovered genes possess the capacity to suppress spontaneous murine lymphoma. Studies of the expression of endogenous ecotropic and xenotropic murine leukemia viruses in mice of these crosses suggest that one of the new genes involved in lymphoma suppression may act by delaying the expression of xenotropic virus. (Author abstract) (25 Refs)

47. ISOLATION OF A KIRSTEN MURINE LEUKEMIA VIRUS MUTANT TEMPERATURE SENSITIVE FOR PARTICLE PRODUCTION AND ENV GENE MINUS.

Horwich A, Dickson C, Ozanne B
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Virology; 118(1):136-147 1982

An NIH/3T3 cell, nonproductively infected with Kirsten murine leukemia virus (Ki-MLV), was isolated shortly after a low multiplicity of infection. The clone, K23, harbors a Ki-MLV genome with two defects: virus particle production is temperature sensitive and no envelope gene products can be detected immunologically. Intracellular Ki-MLV RNA consists of a single species which is of genome size. No Ki-MLV RNA is detected which corresponds to the env gene mRNA. This defect in RNA processing accounts for the lack of gp70 and p15E. The temperature-sensitive lesion may be in processing of Pr65gag or Pr65gag/pol precursor proteins. At 39 or 33 C the cells harbor Pr65gag and Pr180gag/pol. Intracellular p30, however, is only detected in cells at 33 C. At 33 C, the permissive temperature, virus particles are released which have a density of 1.13 g/ml, contain p30, p12, p10, reverse transcriptase, and RNA, but lack gp70 and p15E. At 39 C no particles are detected. Thus, K23 appears to contain a viral genome with mutations which affect processing of both viral proteins and mRNAs. The nature of these defects is discussed. (Author abstract) (31 Refs)

48. ISOLATION OF TWO VARIANTS OF DUAL ECOTROPIC AND XENOTROPIC RETROVIRUS FROM THYMUSES OF MICE INOCULATED AS NEWBORNS WITH GROSS MURINE LEUKAEMIA VIRUS.

Youn JK, Hayat-Santillana M
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Ann Virol; 132(2):207-216 1981

Two variants of dual ecotropic and xenotropic retrovirus isolated from thymuses of C3HeB/Fe mice inoculated ip as newborns with a leukemogenic dose of Gross murine leukemia virus passage A are described. Thymus cells of individual mice were cocultivated with mink murine leukemia viruses (MvlLu). Virus detections were preformed weekly by reverse transcriptase assays with each culture supernatant from the cocultures and by parallel XC tests. By this procedure, the XC negative and mink cell infectious virus Th2P1 was isolated. This virus replicated efficiently in mink MvlLu cells and in mouse SC1 cells. When subconfluent MvlLu cultures were infected with Th2P1, 6-10 days later numerous foci of morphological change characterized by thickened cell sheets surrounded by rounded cells with vacuoles were observed. In C3HeB/Fe mice inoculated ip as newborns with 0.3 ml of the Th2P1 virus suspension, no leukemia developed during 500 days after virus inoculation. Th4P1 was isolated from a mouse free from leukemic symptoms. Host range studies revealed that this virus replicated efficiently in MvlLu, SIRC, NRK, and SCI cells, but not in human breast cancer cells. For mouse cells, Th4P1 showed N tropism, and did not induce any morphological change neither in heterogenous nor in mouse cells. Th4P1 was XC negative, possessed helper activites towards both S+L- mink and S+L- mouse cells, and was neutralized significantly by anti-xenotropic and anti-ecotropic virus serum. (19 Refs)

IMMUNOLOGICAL STUDIES

49. IMMUNE SELECTION OF TUMOR CELL VARIANTS IN CHICKENS BEARING TUMORS INDUCED BY AVIAN SARCOMA VIRUS.

Wainberg MA, Israel E, Yu M
Lady Davis Inst. for Medical Res., Sir Mortimer B. Davis-Jewish General Hosp., Montreal, H3T 1E2 Quebec, Canada
Cancer Res; 42(5):1669-1675 1982

We have compared avian sarcoma cells, cultured from tumors at various stages of growth, in terms of their ability to synthesize infectious progeny virus and to express antigens that are reactive with the sensitized lymphocytes of tumor-bearing host. Cell-mediated immunity in chickens bearing tumors induced by avian sarcoma viruses was monitored by each of a target cell cytotoxicity test and an antigen-driven lymphocyte stimulation assay. Our results show that it is only those tumor cells which have been derived from progressively growing neoplasms that are able to synthesize infectious progeny virus and to specifically interact with the sensitized lymphocytes of tumor-bearing hosts. In contrast, cells from regressing tumors do not express relevant antigens to the same extent as do progressors, and they synthesize noninfectious particles only. Experiments on cellular outgrowths, derived from the plating at limited dilution of progressively growing tumor cells, revealed that such producers of defective virus are present at the earliest stages of tumor growth. Both these cells and regressing tumor cells are poorly stained (about 10%) in indirect immunofluorescence tests by antiserum against viral envelope glycoprotein, whereas tumor cell from progressing neoplasms react well (about 60 to 85%). These results suggest that tumor cells which are found in regressing neoplasms are selected out by a functional immune response directed against cells which are efficient producers of progeny virus. (Author abstract) (24 Refs)

50. NATURAL ANTIBODIES TO THE STRUCTURAL CORE PROTEIN (P24) OF THE HUMAN T-CELL LEUKEMIA (LYMPHOMA) RETROVIRUS FOUND IN SERA OF LEUKEMIA PATIENTS IN JAPAN.

Kalyanaraman VS, Sarngadharan MG, Nakao Y, Ito Y, Aoki T, Gallo RC
(c/o Gallo) Lab Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 79(5):1653-1657 1982

We investigated the involvement (in adult T-cell leukemias and lymphomas) of the human T-cell leukemia virus (HTLV) that was previously isolated in one of our laboratories from cultured T cells of some patients in the United States with leukemias and lymphomas involving relatively mature T cells. High titers of antibodies capable of quantitative precipitation of 125I-labeled p24, a well characterized core protein of HTLV, were detected in 12 of 12 patients with untreated adult T-cell leukemia (ATL). (1 negative was a patient on chemotherapy). Ten of the 12 positive samples were from an area where the disease is endemic. Strong precipitating antibodies were also detected in five of seven cases of T-cell malignant lymphoma (TML) which differs from ATL by having fewer leukemic cells in the peripheral blood. High antibody titers were also observed in one of five cases of acute monoblastic leukemia and one of eight cases of chronic myelogenous leukemia in the blast phase of the disease. Low to moderate titers of antibodies were detected in several categories of leukemia (2 cases of blast-phase chronic myelogenous leukemia, 2 cases of acute lymphoblastic leukemia of the null-cell type, and 1 case of acute myelogenous leukemia). Among all categories of leukemias, except ATL and TML, more cases were negative than positive for anti-p24 activity. All of 79 sera from normal Japanese, including 39 collected from the endemic ATL area of southwest Japan, were negative for antibodies to HTLV p24. All the positive reactivities observed were highly specific to HTLV. The only competition observed in the precipitation of HTLV p24 was with HTLV or with cell lines expressing HTLV and not with various animal retroviruses or a large number of human and subhuman primate cell lines, not known to be producing HTLV. The data strongly indicate an association of HTLV with the increased incidence of ATL in parts of Japan, probably with other forms of leukemias in Japan, and, less commonly, with certain T-cell malignancies in the United States. (26 Refs)

51. ADULT T-CELL LYMPHOMA-LEUKAEMIA IN BLACKS FROM THE WEST INDIES.

Catovsky D, Rose M, Goolden AW, White JM, Bourikas G, Brownell AI, Blattner WA, Greaves MF, Galton DA, McCluskey DR, Lampert I, Ireland R, Bridges JM, Gallo RC
Medical Res. Council Leukaemia Unit, Royal Postgraduate Medical Sch., London, England
Lancet; 1(8273):639-642 1982

Six Black patients (5 born in the West Indies and 1 in Guyana), aged 21-55 yr, had adult T-cell lymphoma-leukemia diagnosed in the UK This disorder is rare in Europe and the USA, but is more common in Japan. Five patients had severe hypercalcemia which correlated with disease activity, although osteolytic lesions were found in only one. Other clinical features were lymphadenopathy and a high white blood-cell count (range 27-67 x 10(9)/l) with a predominance of pleomorphic lymphoid cells with pronounced nuclear irregularities prominent at ultrastructural level. The cells in all cases formed rosettes with sheep red blood-cells and lacked terminal transferase. Analysis with OKT monoclonal antibodies in four cases confirmed a mature T-cell phenotype defined as helper/inducer (T4+, T6-, T8-) in three. Combination chemotherapy resulted in short-lived remissions; four patients died and two have survived 3-6 mo. The disease in these patients is indistinguishable on clinical and pathological grounds from adult T-cell leukemia/lymphoma in Japan. Geographical clustering among certain racial groups suggests common etiological factors in the pathogenesis of this disease. The finding of high titer antibody against the structural core protein (p24) of a new human C-type leukemia virus (human T-cell leukemia/lymphoma virus) in all tested cases from this series and data from all but one case from Japan suggest that one such factor may be viral. (Author abstract) (no Refs)

52. ANTI-TUMOR IMMUNITY IN B-LYMPHOCYTE-DEPRIVED MICE. III. IMMUNITY TO PRIMARY MOLONEY SARCOMA VIRUS-INDUCED TUMORS.

Gordon J, Holden HT, Segal S, Feldman M
Weizman Inst. Science, Rehovot, Israel
Int J Cancer; 29(3):351-357 1982

Tumor induction and immunity to tumors were studied following the injection of Moloney sarcoma virus (MSV) into mice whose B-lymphocyte functions had been suppressed by the chronic administration of anti-IgM antibodies. Two preparations of MSV were used, one which gives rise to tumors which uniformly regress in normal adult mice, and another which elicits progressively growing tumors in the majority of recipients. The tumor incidence, mean tumor size, and tempo of regression were not modified by treatment with anti-IgM. However, whereas tumors induced by the regressor virus were all rejected in 19 NRG-treated and 29 untreated recipients, continued growth was obtained in 2 of 23 B-lymphocyte-deprived mice. Furthermore, in nine additional mice from this group, apparent rejection was followed by tumor recurrence at the site of the initial tumor. Continued growth was accompanied by widespread metastasis. These tumors were freely transplantable to normal syngeneic recipients. Metastasis and transplantability were also detected in 7 of 24 anti-IgM-treated mice given progressor virus, but were not seen in the control animals. Recurrence and metastasis was obtained despite the presence of high levels of specific cytotoxic T lymphocytes in the spleen. It is concluded that B lymphocytes or their products play an essential role in host protection against MSV-induced tumors. (Author abstract) (29 Refs)

53. THE IN VITRO GENERATION OF H-2-RESTRICTED CYTOTOXIC T CELLS TO AKR/GROSS LEUKEMIA VIRUS-INDUCED TUMORS. I. REQUIREMENT FOR STIMULATION WITH ALLOGENEIC LEUKEMIA CELLS IN VIVO.

Green WR
Basic Immunology Program, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
J Immunol; 128(3):1043-1049 1982

We have reported previously that vigorously lytic preparations of H-2-restricted C57BL/6 (H-2b) murine T cells specific for the subset of endogenous AKR leukemia virus-induced tumors that express the Gross cell surface antigen, including EmaleG2, can be raised. The generation of such CTL was accomplished by in vivo priming with an allogeneic AKR leukemic line followed by in vitro coculture of spleen cells from primed mice with irradiated GCSA+ tumors of H-2b haplotype. The results of the present report strongly suggest that the form of primary in vivo stimulation is crucial to the generation of such CTL. Examination of the four GCSA+ tumor cells of H-2b haplotype that are susceptible target cells in this system confirmed the requirement for in vivo alloantigenic stimulation. Thus, the two syngeneic tumor targets, EmaleG2 and EL4(S), were inefficient, whereas two H-2 congenic tumor targets, AKR H-2bSL1 and B.GV (BALB.B-derived), were efficient when used as priming cells. It appeared that the generation of H-2-restricted C57BL/6 CTL to AKR/Gross leukemia virus-induced tumors required concomitant in vivo stimulation with both target antigen and alloantigens. Although these alloantigens were not required to be H-2 encoded, it appeared they had to be present on the same cell that expressed the target antigens to exert their stimulatory effect. (33 Refs)

54. A CRUCIAL ROLE OF THE H-2 D LOCUS IN THE REGULATION OF BOTH THE D- AND THE K-ASSOCIATED CYTOTOXIC T LYMPHOCYTE RESPONSE AGAINST MOLONEY LEUKEMIA VIRUS, DEMONSTRATED WITH TWO DB MUTANTS.

Stukart MJ, Vos A, Boes J, Melvold RW, Bailey DW, Melief CJ
(c/o Melief) Dept. Tumor Immunology, Central Lab. Netherlands Red Cross Blood Transfusion Service, P.O. Box 9190, 1006 AD Amsterdam, The Netherlands
J Immunol; 128(3):1360-1364 1982

Previous studies have shown that the CTL response of C57BL/6(B6,H-2b) mice against Moloney leukemia virus is H-2 Db-restricted. In the current paper, we analyze the role of the H-2 Db locus in the CTL response against Moloney virus with two strains of mice carrying a mutation in the H-2 Db locus: B6.C-H-2bm13(bm13) and B6.C-H-2bm14(bm14). The influence of the D locus was seen at two levels. First, neither of the two Db-mutant targets could be recognized by Db-restricted CTL, as demonstrated with B10.A(4R) (Kk Db) and B6 (Kb Db) effector cells. Second, mutation at the Db locus strongly altered the character of the response, either by causing nonresponsiveness (bm 14 effector) or by increasing the Kb-associated component of the CTL response (bm13 effector). These findings indicate that a single genetic element, H-2 D in this instance, determines the restriction specificity and regulates the magnitude of the CTL response. Cold target inhibition studies showed that either the restriction specificities of Dbm13 and Kb in the CTL response to this virus are indistinguishable or that the Dbm12-associated component of bm13 CTL is negligible. Experiments with (B6 x bm13)F1 and (B6 x bm14)F1 hybrid responding cells demonstrated a decisive role of H-2 on the antigen-presenting cells used for restimulation in vitro: primed F1 responding cells mounted CTL responses with the H-2 preference and magnitude of the parental cell type used for restimulation in vitro. Our findings strongly support the notion that Type I MHC molecules regulate the magnitude and specificity of the CTL response against viruses. (Author abstract) (29 Refs)

55. DEFINITION OF ALIEN H-2 DETERMINANTS ON A FRIEND LEUKEMIA BY ANALYSIS OF ALLOREACTIVITY OF CTL FROM PRIMARY MLC.

Greenberg PD, Cheever MA, Fefer A
Div. Oncology, RK-25, BB 1015 Health Sciences, Univ. Washington, Seattle, WA, 98195
J Immunogenet; 8(6):493-508 1981

An in vivo passaged subline (HFL/d) of Friend virus-induced leukemia of BALB/c origin expressed alien H-2 antigens as determined by reactivity with cytolytic T lymphocytes (CTL). This subline originated from an in vitro passaged subline HFL/d-tc, which when inoculated into BALB/c mice induced weak transplantation resistance. During adaptation to in vivo growth the new ascitic subline HFL/d apparently acquired the capacity to stimulate a cytotoxic response to H-2d antigens, but lost the ability to be lysed by CTL or antisera directed to its H-2d determinants. The presence of H-2d antigen of HFL/d recognizable by CTL was further confirmed by the inhibition of lysis of H-2d targets by HFL/d cold targets. HFL/d stimulated in primary mixed lymphocyte culture (MLC) the generation of CTL which could lyse HFL/d through recognition of non-H-2d determinants not detectable on the parent in vivo passaged subline HFL/d-tc. The alloantigens on HFL/d were typed by generating CTL in primary MLC with HFL/d as stimulator, and measuring reactivity to targets with known H-2 antigens, and was confirmed by assessing recognition of HFL/d targets by CTL generated in primary MLC with stimulators expressing known H-2 antigens. HFL/d expresses Kd and Dd determinants derived from its strain of origin, alien determinants similar to Kb and Db antigens, and at least one additional determinant not present on normal H-2d or H-2b cells. CTL generated in MLC in a sensitive tool for examination of tumors for the presence of alien and/or cross-reactive H-2 determinants. (39 Refs)

56. STUDY OF CELL-MEDIATED IMMUNITY IN B77 TUMOR BEARING RATS BY 51CHROMIUM RELEASE ASSAY.

Kalafut F, Novotna L, Valentova N
Cancer Res. Inst., Slovak Acad. Sciences, 812 32 Bratislava, Czechoslovakia
Neoplasma; 28(6):689-695 1981

Cell immunity was followed in Lewis rats with transplanted syngeneic B77 tumors, by means of the cytotoxic 51chromium release test. Lymphocytes from peripheral blood, or from regional lymph nodes of tumor bearing animals, cocultured for 24 hr with target B77 cells had an enhanced cytotoxic effect on target cells in comparison with lymphocytes of control donors. This effect of the lymphocytes still increased during 48 hr of coculture. (Author abstract) (19 Refs)

57. CELL-MEDIATED IMMUNITY TO VIRAL PROTEINS IN MICE BEARING MOLONEY SARCOMAS.

Koppi TA, Halliday WJ
Dept. Microbiology, Univ. Queensland, St. Lucia, Queensland 4067, Australia
Immunol Lett; 4(3):135-140 1982

Definition of the soluble antigens responsible for in vitro reactivity in the leukocyte adherence inhibition (LAI) assay was studied with extracts and purified viral proteins. Viral proteins were tested in various concentrations with peritoneal cells (PC) from mice bearing tumors induced by Moloney sarcoma virus (MSV). The LAI indicated weak reaction with viral proteins p10 and p12, and significant adherence with gp71 and p30. In order to assess whether blocking factors could be directed against LAI with viral proteins, the normal serum in virus-induced LAI was replaced by serum from tumor-bearing mice. Results with tumor extract, gp71 and p30 showed that LAI was blocked. The effect of depletion of macrophages on the indirect LAI was tested with a MSV tumor extract and the viral protein gp71. Unfractionated PC reacted with both the extract and gp71. Nonadherent cells (lymphocytes) were not reactive with either source of antigen, indicating a requirement for adherent cells (macrophages). These accessory cells could be replaced by normal PC to give restored reactivity. Thus, a non-viral tumor-associated antigen was the active component of the extract. LAI reactivity with both tumor extract and gp71 depended on the presence of accessory adherent cells. (31 Refs)

58. MONOCLONAL ANTIBODIES TO XENOTROPIC AND MCF MURINE LEUKEMIA VIRUSES DERIVED DURING THE GRAFT-VERSUS-HOST REACTION.

Portis JL, McAtee FJ, Cloyd MW
Dept. Health and Human Services, Public Health Service, NIH, Natl. Inst. Allergy and Infectious Diseases, Rocky Mountain Lab., Hamilton, MT, 59840
Virology; 118(1):181-190 1982

The humoral immune response during adult graft-vs-host reaction (GVHR) was assessed by the recovery of antibody-forming host spleen cells using cell fusion techniques. Two parent - F1 strain combinations were studied, (B6 x D2)F1 and (NFS x AKR)F1 injected with the respective parental spleen cells. Hybridomas derived from recipient spleens were found to produce antibody with predominant specificity for murine leukemia virus (MuLV) envelope (env) polypeptides. The recovery of anti-MuLV monoclonal antibodies was dependent on the donor strain. Thus, D2-(B6 x D2)F1 and AKR - (NFS x AKR) resulted in a high incidence of anti-MuLV antibody production among the primary fusion products whereas no anti-MuLV hybridomas were recovered when B6 or NFS, respectively, were used as donors. Hybridomas derived from D2-(B6 x D2)F1 produced anti-MuLV antibodies of two general specificities: (1) broadly reactive, detecting determinants expressed by ecotropic and xenotropic MuLV, and (2) xenotropic MuLV specific. The latter group included antibodies reacting with all xenotropic MuLV and antibodies with xenotropic MuLV strain specificity. Xenotropic MuLV-specific determinants were expressed by gp70, p15(E), and the gp70-p15(E) complex (gp90). This is, to our knowledge, the first report of monoclonal antibodies specific for xenotropic MuLV. In contrast, hybridomas derived from AKR - (NFS x AKR) produced antibodies which reacted predominantly with unique determinants of a subgroup of MCF viruses. These results suggested that the anti-MuLV antibody repertoire expressed during GVHR is influenced by the endogenous MuLV of the respective mouse strain combination. (Author abstract) (25 Refs)

59. EFFECT OF BACILLE CALMETTE-GEURIN IMMUNOTHERAPY ON FELINE SARCOMA VIRUS-INDUCED NEOPLASMS IN THE CAT.

Bachman D, Cockerell GL, De Noronha F, Rapp HJ
Dept. Pathology, New York State Coll. Veterinary Medicine, Cornell Univ., Ithaca, NY, 14853
Am J Vet Res; 43(3):475-480 1982

Kittens infected experimentally with feline sarcoma virus (FeSV) were inoculated with emulsions of bacille Calmette-Guerin (BCG) cell wall preparations to determine the effect of BCG immunotherapy on FeSV-induced sarcomagenesis. The BCG preparations or emulsificant control preparations were administered (i) subcutaneously at the same time and site as was the FeSV inoculation, (ii) at the same site but 1 wk after FeSV inoculation, or (iii) with a mixture of viable autochthonous neoplastic cells approx 35 days after FeSV inoculation. There was no difference in the percentage of kittens that developed neoplasms, the prepatent period for neoplastic development, the percentage of kittens with neoplastic regression, or the survival rate among groups given BCG, emulsificant control, or FeSV alone. Significantly (p less than 0.05) greater dissemination of neoplasms was seen in groups given BCG or emulsificant control preparations, compared with dissemination in groups given FeSV alone. (Author abstract) (25 Refs)

OTHER RELATED STUDIES

60. SPECIFIC ANTIBODY PRODUCTION BY LYMPHOCYTE HYBRIDOMAS.

Sinkovics J
Dept. Virology and Epidemiology, Baylor Coll. Medicine, Houston, TX
Magy Onkol; 26(1):1-6 1982

The development and properties of lymphocyte hybridomas and their specific antibody production are described. Tetraploid mouse lymphoma cells developed were proposed to have emerged through the fusion of a mouse leukemia virus-producing diploid lymphoma cell and an immune plasma cell from the spleens of mice that previously rejected the lymphomas. The tetraploid lymphoma cells were found to produce both leukemia virus and immunoglobulins; the immunoglobulins specifically neutralized the mouse leukemia virus. The tetraploid lymphoma cells grew as ascites tumors in the peritoneal cavity of mice. These tetraploid, specific antibody-producing lymphoid cells are the first published examples of lymphocyte hybridomas. Fusion of this type is suggested to be likely to occur naturally in lymphoproliferative diseases. The examples include Burkitt's lymphoma cells, Reed-Sternberg cells, and giant Sezary's cells. Human hybridomas are expected to be of great therapeutic and theoretical significance. (6 Refs) (In HUN)

61. VARIANTS OF AN INTERSPECIES HYBRIDOMA WITH ALTERED TUMORIGENICITY AND PROTECTIVE ABILITY AGAINST MOUSE MYELOMA TUMORS.

Baumal R, Musclow E, Farkas-Himsley H, Marks A
Dept. Pathology, Hosp. Sick Children, Univ. Toronto, Toronto, Ontario M5G 1X8, Canada
Cancer Res; 42(5):1904-1908 1982

Recent isolates of RX54-3 hybridoma cells (new cells) protect BALB/c mice against subsequent challenge with the tumorigenic myeloma parent cells used to construct this hybridoma. In contrast, hybridoma cells which have been maintained in tissue culture for long periods of time (old cells) are not protective. In the present study, we compared a number of properties of the new and old hybridoma cells and determined which line was more similar to the parent myeloma. We found that new hybridoma cells resembled myeloma cells in: (a) possessing A- and C-type viral particles on transmission electron microscopy and a relatively smooth surface on scanning electron microscopy; (b) being sensitive to a hypotonic solution containing the dye propidium iodide; (c) having similar DNA histograms on flow cytometric analysis; (d) being sensitive to the bacteriocin colicin HSC10; and (e) being tumorigenic in nude mice. In contrast, old hybridoma cells differed in all of these characteristics from new hybridoma and myeloma cells. Therefore, in order to protect against challenge with the tumorigenic myeloma parent, hybridoma cells must retain properties of that parent. (Author abstract) (10 Refs)

62. FURTHER CHARACTERIZATION OF THE CELLS INVOLVED IN LEUKOCYTE ADHERENCE INHIBITION WITH MURINE TUMOR EXTRACTS.

Koppi TA, Halliday WJ
Dept. Microbiology, Univ. Queensland, St. Lucia, Brisbane, Queensland 4067, Australia
Cell Immunol; 66(2):394-406 1982

Peritoneal cells from tumor-bearing CBA mice were depleted of either T lymphocytes (by treatment with anti-Thy-1.2 antiserum), lymphocytes with the Ly-1 marker (by anti-Ly-1.1 monoclonal antibody), or macrophages (by an adherence method). Depleted populations were compared with control populations for their ability to react with the corresponding tumor extract in the leukocyte adherence inhibition (LAI) assay. Direct and indirect assays were used, with emphasis on the latter which depends on the formation of a soluble mediator, leukocyte adherence inhibition factor (LAIF). Both Moloney sarcoma virus-induced tumors and transplanted methylcholanthrene-induced tumors were employed and gave similar results. LAI reactivity depended on lymphocytes with the

Thy-1 and Ly-1 markers, and on macrophages (syngeneic or allogeneic). These T lymphocytes were shown to be the source of LAIF, the macrophages being required as accessory cells. T lymphocytes were also necessary in the LAIF-responsive indicator cell population. (Author abstract) (27 Refs)

63. ANTITUMORAL IMMUNOADJUVANTICITY OF PARIETAL SKELETONS OF CANDIDA ALBICANS AND MI CROCOCCI.

Favalli C, Baccarini M, Blasi E, Bevilacqua R, Rinaldi C, Mastroviti F

Istituto di Microbiologia, Universita degli Studi di Roma, Roma, Italy

Boll Soc Ital Biol Sper; 57(18):1911-1915 1981

Antitumoral immunoadjuvanticities (IA) of Candida albicans (CA) and Micrococcus lysodeiticus (ML) were evaluated as follows. Parietal insoluble glucan fraction or glucan ghost (GG) was prepared from the CA after repeated extractions with alkalies and acids. Ascitic lymphoma LSTRA was induced in Balb/c mice CD2f1 by Maloney virus. The GG of the CA and the parietal skeletons (PS) of the ML were injected ip 14 days before or 1 day after the tumor transplantation (TT). Effect of the antiblastic agent carmustine (BCNU) was evaluated by administering it 5 days after the TT. Control tests were carried out with inactivated whole cells of the CA. The antitumoral effect was evaluated on the basis of median survival time (MST) and long term survival time (LST: 60 days after the TT), using the Mann-Whitney test. The MST was increased somewhat only with the whole cells of the CA; neither the GG nor the PS had any effect in the absence of the BCNU. The IA was evident in the presence of the BCNU, increasing with dosage (10.8, 18, and 30 mg/kg); this effect was most pronounced when whole cells of the CA were used, with MST of 16%, 30% and 60% and LST of 0%, 25%, and 56% respectively, for the increasing dosages of BCNU . (3 Refs) (In ITA)

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VIRUS ISOLATION AND CHARACTERIZATION

1. BIOLOGICAL CHARACTERISTICS OF TYPE C VIRUSES ISOLATED FROM DIFFERENT FRIEND ERYTHROLEUKAEMIC CELLS.

Vinton EC, Woytowicz JM, Levy SB
(c/o Levy) Cancer Res. Center, Dept. Medicine, Tufts Univ. Sch. Medicine, Boston, MA, 02111
J Gen Virol; 59(part1):73-81 1982

We have examined the expression of Type C RNA viruses in different Friend erythroleukemic cell types, distinguished on the basis of increasingly malignant characteristics, which arise during the aging of mice inoculated with the polycythemic Friend virus complex. Most early appearing Friend cells (Type I) expressed ecotropic virus, but cells of later malignant types showed decreased and variable expression. In general, the

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more malignant cells released less ecotropic virus. Xenotropic virus was detected in low numbers from Type I, II, and IV cells. Two viruses were cloned from Type II tumor cells: a xenotropic virus (II clone 1) and an N-tropic ecotropic virus (II clone 2). No pathogenic activity was found when II clone 1 was inoculated into newborn and adult DBA/2J and NIH/Swiss mice observed for up to 20 mo, where II clone 2 caused a rapid anemic erythroleukemia in both N- and B-type newborn mouse strains. It caused a similar form of leukemia in susceptible N-type adult mice, but at a lower frequency and with a longer latency (usually greater than 5 mo). This finding demonstrated a lack of NB restriction in newborn mice. The virus was much less active in DBA/2J mice from which it had been originally cloned; it also appeared to cause lymphoma or to shorten the latency of spontaneous lymphoma in DBA/2J mice. (Author abstract) (38 Refs)

2. INDUCTION OF ERYTHROID TUMORIGENIC COLONIES BY FRIEND HELPER VIRUS F-MULV ALONE AND ISOLATION OF A NEW CLASS OF FRIEND ERYTHROLEUKEMIC CELLS.

Shibuya T, Mak TW
(c/o Mak) Ontario Cancer Inst., Univ. Toronto, Toronto, Ontario M4X 1K9, Canada
J Cell Physiol; Suppl1:185-194 1982

Induction of pathological and cellular changes by cloned Friend murine leukemia virus (F-MuLV) and induction of tumorigenic erythroleukemic cells and Friend virus colony forming units (CFU-FV) by cloned F-MuLV were studied in BALB/c mice. Increased spleen wt could be detected 5-6 wk after injection of the cloned F-MuLV, accompanied by an onset of anemia with hematocrit dropping to 20% or less. The decrease in hematocrit was accompanied by an increase in the mortality rate in the infected mice. No tumorigenic colonies could be detected in spleens of the mice prior to their deaths which occurred in approx 12 wk. At biweekly intervals from 10-14 wk after infection, 0.5 ml of packed RBC from uninfected BALB/c mice were injected iv into the infected mice. The cells from the enlarged spleens were then transplanted into uninfected BALB/c adult mice. Splenomegaly developed in the recipient mice within 3 wk of transplantation. After two such serial transplants, the spleens were cultured for Friend erythroleukemia cell lines (FCL) and were found to contain them. The morphology of F-MuLV induced CFU-FV was more diffuse in appearance than that obtained from FV-P or FV-A infected spleens. The cells resembled erythroblasts when examined with Wright-Giemsa stain. None of the colonies examined released any detectable replication defective spleen focus forming viruses (SFFV) and the colonies were erythroid in nature. F-MuLV alone, without the SFFV component, can induce a malignant phase of the Friend disease in newborn BALB/c or NIH Swiss mice. (31 Refs)

3. CHILDREN'S BRAIN TUMOUR CELLS PRODUCE RNA PARTICLES WITH INCOMPLETE RETROVIRUS CHARACTERISTICS.

Thorne HJ, Jose DG, Adams FC, Coelen RJ, Whitehead RH, Klugg G
Clinical Immunology and Immunogenetics Unit, Cancer Inst., Melbourne, Victoria, Australia
Oncology; 39(3):156-162 1982

Short-term cultures of cells from human brain tumors have been reported to synthesize RNA particles of density in the range characteristic of C type RNA retroviruses, with associated DNA polymerase activity. Fresh tumor cells obtained from six children with astrocytoma and seven children with medulloblastoma, together with one sample of normal brain tissue and normal leukocytes from brain tumor patients were assayed by several characteristics for the presence of primate retrovirus. One of six (17%) astrocytomas and four of seven (57%) medulloblastomas released RNA particles which banded in sucrose gradients at a density of 1.16-1.18 g/cm3 together with a short segment of DNA, which was eliminated by prior ribonuclease treatment and two proteins of 28k and 16k daltons. These findings were compatible with the presence of a primate retrovirus. Immune coprecipitation of 125I-labeled proteins from the 1.16-1.18 g/cm3 gradient region failed to show any reactivity with antisera to p28 core antigens or the p70 reverse transcriptase antigens of simian sarcoma virus, baboon endogenous virus or Mason Pfizer virus. Assays for DNA polymerase activity in culture supernatant fluid showed only a low amount of activity with template preference not characteristic of the retroviral reverse transcriptase enzyme. (Author abstract) (21 Refs)

4. THE STRUCTURE OF THE ROUS SARCOMA VIRUS GLYCOPROTEIN COMPLEX: IN VITRO PHENOTYPIC MIXING OF ROUS SARCOMA VIRUS.

Pauli G, Friis R
Institut fur Virologie, Freie Universitat Berlin, Nordufer 20, D-1000 Berlin 65, W. Germany
Arch Virol; 71(2):141-148 1982

Gp85 the major envelope glycoprotein of Rous sarcoma virus can be released from intact VIRUS by treatment with 2-mercaptoethanol. Attempts were made to reassociate released gp85 to 2-mercaptoethanol treated virus. In order to study the biological activity and to analyze the reaction product with biochemical methods gp85 from a subgroup different from the recipient virus was used. Successful in vitro phenotypic mixing could be shown. The biochemical analysis, however, revealed that no reassociation of gp85 and gp35 could be obtained. The biological activity was due to a strong association of whole gp85-gp35 molecules derived from the gp85 preparation to the recipient virus. These molecules were present as a minor contaminant in the gp85 preparation. (Author abstract) (7 Refs)

VIRUS ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

5. NOVEL LOCALIZATION OF PP60SRC IN ROUS SARCOMA VIRUS-TRANSFORMED RAT AND GOAT CELLS AND IN CHICKEN CELLS TRANSFORMED BY VIRUSES RESCUED FROM THESE MAMMALIAN CELLS.

Garber EA, Krueger JG, Goldberg AR
Rockefeller Univ., New York, NY, 10021
Virology; 118(2):419-429 1982

We have investigated by indirect immunofluorescence and subcellular fractionation the intracellular location of pp60src in RSV-transformed mammalian cells and in CEF cells transformed by virus rescued from these cells. Two independently derived cell lines were examined: RR1022 cells isolated from an in vivo sarcoma induced in an Amsterdam rat by infection with SR-RSV-D; and Pcl, cells isolated from a soft agar colony of normal goat skin fibroblasts transformed in vitro by SR-RSV-D. Transforming viruses (RSV-RR and RSV-Pcl) were rescued from RR1022 and Pcl cells by fusion with CEF

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cells. Immunofluorescence microscopy showed association of pp60src with the nuclear envelope and the juxtanuclear reticular membranes in the transformed mammalian cells and in CEF cells transformed by the rescued viruses, in contrast to the plasma membrane localization of pp60src seen in SR-RSV-transformed CEF cells. Results of subcellular fractionation by differential centrifugation and fractionation of particulate fractions by equilibrium centrifugation in discontinuous sucrose gradients were in agreement with the differences in pp60src distribution observed by immunofluorescence microscopy. Although the mammalian cell lines were independently derived, pp60srcs isolated from RR1022 and Pcl cells both lacked amino-terminal 21-and 18-kilodalton [35S]methionine S aureus V8 protease peptides found in SR-RSV-D pp60src. Proteolytic peptides identical to those of pp60src from the mammalian cells were obtained from pp60src proteins isolated from rescued virus-transformed CEF cells, suggesting that the alteration in the amino-terminal half of the src protein represents a stable change, and that an alteration in the primary structure of pp60src is responsible for the altered intracellular membrane localization of pp60src in these cells. (Author abstract) (25 Refs)

6. MULTIPLE IMMUNOGLOBULIN HEAVY-CHAIN GENE TRANSCRIPTS IN ABELSON MURINE LEUKEMIA VIRUS-TRANSFORMED LYMPHOID CELL LINES.

Alt FW, Rosenberg N, Enea V, Siden E, Baltimore D
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
Mol Cell Biol; 2(4):386-400 1982

The immunoglobulin heavy-chain proteins and RNAs produced by a large number of Abelson murine leukemia virus (A-MuLV) transformants were analyzed. A variety of mu (u)-related RNA species and gamma-related species were found in these cells. The productive RNAs were termed Pu-RNA; the aberrant RNAs, Au-RNAs; and the sterile RNAs, Su-RNAs. These three classes of Cu-containing RNA species in A-MuLV transformants were characterized. The data support the concept that heavy-chain allelic exclusion is a consequence of feedback control from cytoplasmic u chains and is not controlled at the DNA or RNA levels. (53 Refs)

7. ALTERED EPIDERMAL GROWTH FACTOR (EGF)-STIMULATED PROTEIN KINASE ACTIVITY IN VARIANT A431 CELLS WITH ALTERED GROWTH RESPONSES TO EGF.

Buss JE, Kudlow JE, Lazar CS, Gill GN
(c/o Gill) Dept. Medicine, Div. Endocrinology, Univ. California San Diego Sch. Medicine, La Jolla, CA, 92093
Proc Natl Acad Sci USA; 79(8,part1):2574-2578 1982

To determine the role of epidermal growth factor (EGF)-stimulated protein kinase in the biological effects caused by EGF, tyrosine-specific kinase activity has been quantitated in A431 human epidermoid carcinoma cells and six variant cell lines. Because EGF inhibited proliferation of A431 cells, variants resistant to this inhibition were selected by treatment with mutagen and maintenance for 1 month in 0.1 uM EGF. After cloning and growth for 6-20 generations without EGF, the resistance of the variants to the growth-inhibitory effect of EGF was confirmed. Whereas EGF increased cellular phosphotyrosine content approx 10-fold in parental A431 cells, EGF caused smaller or undetectable increases in the six variant cell lines. Solubilized membranes from the six variants displayed diminished EGF-stimulated phosphorylation of the EGF receptor and of antibodies to p60src (the product of the Rous sarcoma virus transforming gene), which act as an exogenous substrate. The decrease in EGF-stimulated tyrosine-specific protein kinase activity varied from approx 40% (Clone 16) to approx 8% (Clone 18) of parental A431 activity. Phosphorylated EGF receptors from parental and variant cells migrated identically on sodium dodecyl sulfate/polyacrylamide gels. The number of EGF receptors in variant cells decreased in parallel with EGF-stimulated protein kinase activity, so that the specific activity of EGF-stimulated protein kinase per EGF receptor remained constant in the six variant cell lines with reductions in both activities to as low as 10%. These results suggest that this tyrosine-specific protein kinase activity mediates the growth-inhibitory effect of EGF on A431 cells and that both EGF binding and kinase activities reside in the same or tightly associated molecules. (Author abstract) (30 Refs)

8. HORMONE-DEPENDENT TERMINAL DIFFERENTIATION IN VITRO OF CHICKEN ERYTHROLEUKEMIA CELLS TRANSFORMED BY TS MUTANTS OF AVIAN ERYTHROBLASTOSIS VIRUS.

Beug H, Palmieri S, Freudenstein C, Zentgraf H, Graf T
Inst. Virus Res., German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
Cell; 28(4):907-919 1982

Chicken erythroblast cell strains and a cell line transformed by ts mutants of avian erythroblastosis virus (AEV) terminally differentiate when shifted to the nonpermissive temperature (42 C). The differentiated cells resemble mature erythrocytes with respect to morphology and ultrastructure, expression of differentiation-specific cell-surface antigens, pattern of protein synthesis and hemoglobin content. Terminal differentiation is dependent on conditions favoring the differentiation of normal erythroid progenitor cells, including an erythropoietin-like factor. Colonies of ts AEV cells grown at 42 C in semisolid medium resemble erythrocyte colonies derived from normal erythroid progenitor cells. The colonies obtained were comparable in size or slightly larger than the late erythroid precursor (CFU-E) colonies. These results suggest that AEV-transformed cells are blocked at a stage of differentiation that is more advanced than that of the uninfected target cells. ts AEV cells are irreversibly committed to terminal differentiation within 20 to 30 hr after shift to 42 C. (Author abstract) (42 Refs)

9. TARGET CELLS INFECTED BY AVIAN ERYTHROBLASTOSIS VIRUS DIFFERENTIATE AND BECOME TRANSFORMED.

Samarut J, Gazzolo L
Rockefeller Univ., New York, NY, 10021
Cell; 28(4):921-929 1982

Transformation in vitro of bone marrow cells by avian erythroblastosis virus (AEV) gives rise to rapidly growing cells of erythroid nature. Target cells of neoplastic transformation by AEV are recruited among the early progenitors of the erythroid lineage, the burst-forming units-erythroid (BFU-E). They express a brain-related antigen at a high level and an immature antigen at a low level. We show that AEV-transformed cells express low levels of the brain antigen and high levels of the immature antigen. Their response to specific factors regulating the erythroid differentiation indicates that they are very sensitive to erythropoietin. Furthermore, cells transformed by a temperature-sensitive mutant of AEV differentiate into hemoglobin-synthesizing cells 4 days after being shifted to the nonpermissive temperature. All these properties are similar to those of late progenitors of the erythroid lineage, the colony-forming units-erythroid (CFU-E). These results indicate that the AEV-transformed cells are blocked in their differentiation at the CFU-E stage. (Author abstract) (36 Refs)

10. ERYTHROBLAST CELL LINES TRANSFORMED BY A TEMPERATURE-SENSITIVE MUTANT OF AVIAN ERYTHROBLASTOSIS VIRUS: A MODEL SYSTEM TO STUDY ERYTHROID DIFFERENTIATION IN VITRO.

Beug H, Doederlein G, Freudenstein C, Graf T
Inst. Virology, German Cancer Res. Center, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany
J Cell Physiol; Suppl1:195-207 1982

The establishment and characterization of a continuous erythroblast cell line (HD3) that retained its capacity to differentiate in response to a temperature shift in an erythropoietin-like factor dependent fashion and the characterization of variant HD3 sublines are described. A continuous cell line (LSCC HD3) was obtained from a culture of ts34-avian erythroblastosis virus (AEV) clone A6 nonproducer cells that had been in crisis for more than 4 mo. LSCC HD3 has been kept in continuous culture for more than 2 yr. The line does not synthesize helper virus-related proteins, but synthesizes large amounts of p75 AEV, the putative transforming protein of AEV. In four HD3 sublines, 75-85% of the cells became strongly benzidine positive after shift to 42 C. The amount of hemoglobin synthesized by these sublines corresponded to those obtained from ts34-AEV-erythroblast strains analyzed in parallel. Results showed that it is possible to isolate HD3 sublines that resemble freshly transformed ts34-AEV-erythroblast strains in their potential to differentiate. Four cell types (erythrocytes, late and early reticulocytes, and erythroblasts) could be distinguished after induction of terminal differentiation in HD3 sublines. A significant proportion of the cells from sublines 2, 32, 40, and 41 differentiated into more mature forms, including erythrocyte-like cells. Results indicated that the same HD3 variant sublines that were unable to produce hemoglobin upon temperature shift in growth medium plus 10(-5) M hemin were also refractory to temperature-induced terminal differentiation. In all sublines inducible with butyric acid, the amounts of hemoglobin detected with the assay which measures hemoglobin of adult and primitive erythrocytes were much larger than those detected with the assay which predominantly detects adult hemoglobins. (32 Refs)

11. LEVELS OF COLONY-STIMULATING AND INHIBITING ACTIVITIES IN CHICKS WITH MYELOBLASTIC LEUKEMIA ARE RELATED TO DISEASE PROGRESSION.

Bryant DL, Smith RE, Dodge WH
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Exp Hematol; 10(3):249-255 1982

Chicks with myeloblastic leukemia induced by avian myeloblastosis virus (AMV) exhibited increased levels of plasma granulocyte/monocyte (GM) colony-stimulating activity (CSA). Chromatography of plasma from AMV-infected chicks revealed that this CSA eluted in the first protein peak from a column of Sephadex G-200. A second protein peak from the same column contained an inhibitor of GM colony-formation. The presence of the inhibitor and the increased CSA was studied during the development of myeloblastic leukemia. The disease course was separated into two distinct phases: (1) an early phase characterized by the onset of viremia, the induction of leukemic colony-forming cells (CFC) is the marrow, and moderately increased marrow cellularity, (2) a late phase characterized by marked increases in the early parameters, dramatic increases in the number of myeloblasts and decreases in the number of erythrocytic cells. Induction of the GM-CFC-inhibitor occurred during the initial stages of the first phase. Increased GM-CSA occurred later in this phase. We conclude that induction of the inhibitor and increased CSA were associated with disease progression rather than ancillary characteristics of frank disease. (Author abstract) (17 Refs)

12. A HOST GENE CONTROLLING EARLY ANAEMIA OR POLYCYTHAEMIA INDUCED BY FRIEND ERYTHROLEUKAEMIA VIRUS.

Shibuya T, Mak TW
Ontario Cancer Inst., Univ. Toronto, Ontario M4X 1K9, Canada
Nature; 296(5857):577-579 1982

Two isolates of Friend erythroleukemia virus (FLV), FV-A and FV-P (which was derived from FV-A), have varying hematological effects in regard to hematocrit, polycythemia, and the kinetics of erythropoiesis. Further studies are presented which demonstrate that in addition to the viral contributions, host genes play an important part in determining the nature of the disease induced by FV-A or FV-P. A new host gene which determines the induction of early anemia or polycythemia by FLV is described. (23 Refs)

13. EFFECTS OF METALLOPORPHYRINS ON HEMOGLOBIN FORMATION IN MOUSE FRIEND VIRUS-TRANSFORMED ERYTHROLEUKEMIA CELLS. STIMULATION OF HEME BIOSYNTHESIS BY COBALT PROTOPORPHYRIN.

Chang CS, Sassa S
Rockefeller Univ., New York, NY, 10021
J Biol Chem; 257(7):3650-3654 1982

Mouse Friend virus-transformed erythroleukemia cells in culture undergo erythroid differentiation when treated with a variety of compounds including iron protoporphyrin IX, ie hemin. Exogenous hemin is not only incorporated into hemoglobin in these cells but also stimulates heme biosynthesis. In this study, we examined whether metalloporphyrins other than hemin can also induce differentiation, and if so, whether they can also be incorporated into hemoglobin. Among eight metalloporphyrins examined in culture of these cells, ie Co, Mn, Cu, Mg, Ni, Zn, Sn, and Cd protoporphyrin IX, only Co protoporphyrin (10(-4) M) was found to significantly increase the biosynthesis of heme and hemoglobin. In contrast to hemin-mediated induction of erythroid differentiation, Co protoporphyrin was not incorporated into hemoglobin in Friend cells. These data indicate that Co protoporphyrin induces the formation of heme and hemoglobin in Friend cells and that these increases are due to the enhancement of heme biosynthetic activity. (Author abstract) (31 Refs)

14. FRIEND ERYTHROLEUKEMIA VIRUS COMPLEX: ROLE OF VIRAL COMPONENTS IN MODIFYING ERYTHROID DIFFERENTIATION IN MICE.

Fagg B, Ostertag W
Dept. Microbiology, Univ. California, Irvine, CA, 92717
JNCI; 68(3):457-460 1982

The present study was carried out to determine which component of the polycythemic strain of Friend erythroleukemia virus (FV-P) - Friend helper virus [Friend murine leukemia virus (F-MuLV)] or the replication-defective spleen focus-forming virus (SFFV) - is responsible for inducing erythropoietin-independent erythropoiesis and expansion of the erythroid compartment in infected mice. F-MuLV and SFFV were cloned in SC1 cells to give a cell line 643/22N, which released only F-MuLV and SC204, a nonproducer cell line carrying SFFV. On superinfection with specific helper viruses, SC204 yielded further cell lines, which released SFFV in conjunction with (1) Friend, (2) Moloney, or (3) Gross helper viruses. With the use of an in vitro colony formation assay to monitor erythropoiesis in the bone marrow of inbred DBA/2J mice infected with any of the virus preparations containing SFFV plus helper virus, the erythroid precursor cell population was found to become erythropoietin-independent and amplified; adult mice infected with any of the helper viruses alone did not develop any symptoms of Friend disease. Thus the biologic activity of the FV-P complex was unaffected by replacement of the F-MuLV with an unrelated helper virus (Moloney or Gross). These results indicated that the SFFV component of FV-P is responsible for modifying erythroid differentiation in adult mice. (Author abstract) (22 Refs)

15. THE RELATIONSHIP BETWEEN DIFFERENTIATION OF FRIEND ERYTHROLEUKEMIA CELLS AND SYNTHESIS OF PLASMA MEMBRANE-BOUND GLYCOPROTEINS.

Bosman GJ, Boer P, Steyn-Parve EP
Lab. for Physiological Chemistry, State Univ. Utrecht, Vondellaan 24A, 3521 GG Utrecht, The Netherlands
Protides Biol Fluid Proc Colloq; 29:67-70 1982

Changes that plasma membrane-bound glycoproteins go through during dimethyl sulfoxide (DMSO)-induced differentiation of Friend virus-transformed murine erythroleukemia cells (FELC) are reported. When FELC were induced with DMSO in the presence of tunicamycin, Hb synthesis was inhibited, seemingly by arresting the cells just before they became irreversibly committed to differentiation. Results suggest that changes in synthesis of plasma membrane-bound glycoproteins may play a role in the differentiation of Friend erythroleukemia cells. (11 Refs)

16. LACK OF TROPOMYOSIN CORRELATES WITH THE ABSENCE OF STRESS FIBERS IN TRANSFORMED RAT KIDNEY CELLS.

Leonardi CL, Warren RH, Rubin RW
Dept. Anatomy and Cell Biology, Univ. Miami Sch. Medicine, P.O. Box 016960, Miami, FL, 33101
Biochim Biophys Acta; 720(2):154-162 1982

We have utilized epithelial rat kidney cells and their Kirsten viral transformant (442) to examine the role of actin-binding proteins in cellular morphogenesis. Normal rat kidney cells are well spread while the transformed cells are more spherical, poorly adherent, and lack actin stress fibers. By immunofluorescence, anti-tropomyosin prominently stains normal rat kidney cell stress fibers while only a weak, nonspecific fluorescence is observed in 442 cells. Using two-dimensional gel electrophoresis, tropomyosin can be detected in normal rat kidney cell homogenates. The tropomyosin subunits are enriched in Triton-extracted filamentous normal rat kidney cell models, and in extracts of normal rat kidney cell homogenate produced by using a rapid myosin affinity technique to isolate actin and actin-associated proteins. The identity of the tropomyosin subunits has been confirmed by electrophoretic mobility, lack of proline, and the peptide map generated by limited proteolysis. None of these techniques have detected tropomyosin in the corresponding 442 preparations. Our results suggest that transformation of normal rat kidney cells has led to an overall reduction in tropomyosin content. This may be related to the inability of 442 cells to organize filamentous actin stress fibers. (Author abstract) (37 Refs)

17. ALTERATION OF ACTIN CYTOSKELETON WITH TRANSFORMATION AND NEOPLASTIC PROGRESSION OF LIVER EPITHELIUM IN CULTURE.

Troianovskii SM, Bannikov GA
Lab. Mechanisms Carcinogenesis, All-Union Oncological Res. Center of USSR Acad. Medical Sciences, Moscow, USSR
Tsitologiia; 24(2):195-199 1982

Two types of changes in actin distribution pattern in the cytoskeleton were detected during the in vitro transformation of rat hepatic epithelium: reduction of inner bundles in all cells and appearance of marginal actin bundle in central cells (Type A), and reduction of marginal bundle and presence of inner bundles, preferentially oriented along the longer axis of the cells which became more polarized (Type B). Secondary redistribution of actin bundle toward Type B occurred in tumor cells arising from transformed epithelium with Type A actin pattern. High activity of gamma-glutamyl transpeptidase was found in such cells. (11 Refs) (In RUS)

18. ROUS SARCOMA VIRUS TRANSFORMED CELLS ARE RESISTANT TO CYCLIC AMP.

Roth CW, Singh T, Pastan I, Gottesman NM
Lab. Molecular Biology, NCI, Building 37, Room 2E24, Bethesda, MD, 20205
J Cell Physiol; 111(1):42-48 1982

Rous sarcoma virus (RSV)-transformed Chinese hamster ovary (CHO) cells were found to differ from spontaneously transformed CHO cells in their sensitivity to growth inhibition or changes in cell shape induced by 8-Br-cyclic AMP (BrcAMP) treatment. RSV-transformed rat (NRK) cells were also observed to have reduced sensitivity to BrcAMP. These results indicate that transformation of CHO and NRK cells by RSV alters the cells in a different manner than spontaneous transformation. (31 Refs)

19. DISTRIBUTION OF MAMMARY GLAND NEOPLASMS AND FACTORS INFLUENCING METASTASES IN HYBRID MICE.

Sheldon WG, Owen K, Weed L, Kodell R
Pathology Services Project, Natl. Center Toxicological Res., Jefferson, AR, 72079
Lab Anim Sci; 32(2):166-168 1982

Mammary neoplasms in yellow (C3H x VY-Avy)F-1 virgin female mice with the murine mammary tumor virus were distributed equally between the left and right sides. The ratio of thoracic to inguinal gland involvement was 6.4 to 3.6 indicating that the Avy mutation, which enhances age-specific mammary tumor incidence, apparently does not affect the distribution of mammary tumors. The av tumor size was similar in all mammary glands. Multiple tumors occurred 7x more frequently in the thoracic than in the inguinal glands. Metastases occurred more frequently in moribund mice than in those killed at a scheduled time, and the incidence of pulmonary metastases in both groups was associated with the duration of the mammary tumors, their size, their location, and the number of neoplasms. Adenocarcinomas in the thoracic glands metastasized to the lungs more frequently than those in the inguinal glands. (Author abstract) (7 Refs)

20. STUDY OF STORAGE IRON IN CULTURED CHICK EMBRYO FIBROBLASTS AND RAT GLIOMA CELLS, USING MOSSBAUER SPECTROSCOPY.

Bauminger ER, Cohen SG, Ofer S, Bachrach U
Racah Inst. Physics, Hebrew Univ., Jerusalem, Israel
Biochim Biophys Acta; 720(2):133-140 1982

The 57Fe Mossbauer spectra of normal and Rous sarcoma virus-infected cultured chick embryo fibroblasts and rat glioma cells have been measured between 0.08 and 318 K. Ferritin-like iron and bacterio-ferritin-like iron have been found in these cells, in various relative amounts, indicating a close relationship between the two storage materials. The bacterio-ferritin-like iron was found to be predominantly membrane-bound. Above 260 K very wide lines were observed in the Mossbauer spectra, yielding an effective viscosity of about 1 poise in the normal chick embryo fibroblasts and about 0.5 poise in the virus-infected chick embryo fibroblasts. (Author abstract) (12 Refs)

VIRUS REPLICATION AND EXPRESSION

21. GENETIC INTERACTIONS IN INDUCTION OF ENDOGENOUS MURINE LEUKEMIA VIRUS FROM LOW LEUKEMIC MICE.

McCubrey J, Risser R
McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Cell; 28(4):881-888 1982

The frequency of ecotropic murine leukemia virus (MuLV) production in cells induced with halogenated pyrimidines has been investigated in several low leukemic strains of mice. Very few BALB/c or C57BL/6 (B6) induced embryo cells produce MuLV; this low frequency increases 10 to 50 fold in cells of the BALB/c x B6 F1 hybrid. Data from backcrosses of the F1 hybrid to each parent and from BALB/c x B6 recombinant inbred strains indicate that the phenotype of enhanced MuLV production results from interaction of two unlinked loci, dominant (+/+) alleles of which are carried by either parent. Genetic tests with BALB/c x B6 recombinant inbred strains confirm this two-locus model. The loci are designated Inc-1 and Inb-1 to signify their phenotypic detection by induction and the BALB/c or B6 strain of origin, respectively. Examination of hybrids of BALB/c and of B6 with other strains indicates that strains related in pedigree to BALB/c carry Inc-1, whereas those related to B6 carry Inb-1. Identification of genetic loci that specifically interact to enhance MuLV production after exposure to halogenated pyrimidines indicates the existence of mechanisms that regulate the induction or intracellular expression of endogenous MuLV. (Author abstract) (31 Refs)

22. EXPRESSION OF NORMAL LYMPHOCYTES OF TWO CELL SURFACE ANTIGENS, XENCSA AND GIX, RELATED TO THE MAJOR GLYCOPROTEINS (GP70) OF MURINE LEUKEMIA VIRUSES.

Morse HC, Taylor BA, Kozak CA, Chused TM, Sharrow SO, Hartley JW, Stockert E
Lab. Microbial Immunity, Natl. Inst. Allergy and Infectious Diseases, NIH, Building 5, Room 218, Bethesda, MD, 20205
J Immunol; 128(5):2111-2115 1982

XenCSA and GIX are two cell surface antigens related to the major envelope glycoproteins (gp70) of murine leukemia viruses. The levels of expression of these gp70 determinants were assessed in 36 recombinant inbred mouse strains and selected backcrosses derived from crosses between C57BL/6 with DBA/2 and C3H/He. These two antigens segregated in backcross mice and showed a different strain distribution pattern among the recombinant inbred mice, demonstrating that XenCSA and GIX are distinct genetic markers for different endogenous gp70 sequences. It was also shown that independent sets of genes regulate the expression of XenCSA and GIX. (Author abstract) (31 Refs)

23. DIFFERENTIATION AND VIRUS EXPRESSION IN BALB/MO MICE: ENDOGENOUS MOLONEY LEUKEMIA VIRUS IS NOT ACTIVATED IN HEMATOPOIETIC CELLS.

Fiedler W, Nobis P, Jahner D, Jaenisch R
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Proc Natl Acad Sci USA; 79(6,part1):1874-1878 1982

The endogenous Moloney leukemia virus (M-MuLV) in the BALB/Mo substrain of mice is activated during the 1st wk after birth. Virus replication occurs in cells of the lymphatic system. Lymphoid cells therefore represent the target cells for virus replication and leukemic transformation. To investigate whether virus activation occurs during lymphoid cell differentiation, hematopoietic stem cells carrying the endogenous Mov-1 genome were transplanted to sublethally irradiated BALB/c mice. Effective colonization of the recipients was demonstrated by Southern DNA hybridization. No activation of the endogenous Mov-1 genome occurred during a 4-mo observation period after the transplantation. Thus, the first step in development of disease in BALB/Mo mice involves activation of the Mov-1 locus in a nonhematopoietic cell followed by superinfection of lymphatic cells and subsequent virus replication and virus spread. (Author abstract) (20 Refs)

24. VIRAL EXPRESSION IN TWO MYELOMONOCYTIC CELL LINES OBTAINED FROM LONG-TERM BONE MARROW CULTURE INFECTED WITH THE FRIEND POLYCYTHEMIA-INDUCING VIRUS (FV-P).

Mathieu-Mahul D, Heard JM, Fichelson S, Gisselbrecht S, Sola B, Larsen CJ
(c/o Larsen) Lab. de Pharmacologie Experimentale, (U.107 INSERM-LOI-CNRS), Dept. d'Oncologie Experimentale, Centre Hayem, Hopital Saint-Louis, 2 place du Dr. Fournier, 75475 Paris Cedex 10, France
Virology; 119(1):59-67 1982

Two subclones of monomyelocytic cell lines (317 and G-31), issued from mouse long-term bone marrow cultures infected with Friend polycythemia-inducing virus, were studied for virus release and viral protein expression. The 317 cell line permanently produced biologically active spleen focus-forming virus (SFFV) and expressed the gp52SFFV which has been described as encoded by the SFFV genome. In contrast, the G-31 cell line was devoid of any SFFV expression although it released Friend helper leukemia virus (F-MuLV). Both lines expressed a new gp70-related glycoprotein with an apparent mol wt of 66,000. This gp66 species was metabolically unstable and was not packaged into viral particles nor released in culture medium. It was recognized by an anti-Rauscher gp70 antiserum but not by anti-MCF gp70 or anti-p15E antisera. gp66 was not found in erythroblastic Friend tumor cell lines, in fibroblasts infected with virus released by lines 317 and G-31, or in nonmyelomonocytic infected hematopoietic cells. However, it was constantly observed in cell lines with a myelomonocytic origin established in vivo and in vitro. Therefore, gp66 is a F-MuLV gp70-related product specifically linked to the myeloid lineage. (Author abstract) (23 Refs)

25. ACTIVATION OF AN ENDOGENOUS MOUSE TYPE C VIRUS BY UV-IRRADIATED MURINE CYTOMEGALOVIRUS.

Sergiescu D
Institut National de la Sante et de la Recherche Medicale, U.43, Hopital Saint-Vincent-de-Paul, 74, Avenue Denfert-Rochereau, 75014 Paris, France
Int J Cancer; 29(4):459-464 1982

Infection of Kirsten sarcoma virus-transformed non-producer BALB-3T3 mouse cells with UV-irradiated mouse cytomegalovirus (MCMV) resulted in activation of a xenotropic Type C virus detected by infectious center formation in permissive rat or mink cells. The levels of Type C virus activated by MCMV were related to the UV dose applied. Unter optimal conditions the frequencies of activation varied from 3.0 to 8.0 x 10(-4). The capacity of MCMV to activate Type C virus was abolished by heat inactivation and by neutralization with specific antiserum against MCMV. Virus induction decreased under conditions of cell exposure to hydroxyurea or actinomycin D, inhibitors of DNA and RNA synthesis, respectively, with actinomycin D having a greater inhibitory effect. This suggests that both DNA and RNA synthesis are required for UV-MCMV induction of murine xenotropic virus. (Author abstract) (33 Refs)

26. ROLE OF NATURAL PROSTAGLANDINS IN THE CONTROL OF MURINE MAMMARY TUMOR VIRUS EXPRESSION.

Svec J, Svec P, Halcak L, Thurzo V
Cancer Res. Inst., Slovak Acad. Sciences, Csl. armady 21, CSSR-880 32 Bratislava, Czechoslovakia
J Cancer Res Clin Oncol; 103(1):55-67 1982

The regulation of murine mammary tumor virus (MuMTV) production by mammotropic hormones, hormonomimetic substances, and cyclic nucleotides was investigated. The virus produced in control and treated mammary tumor cell cultures was quantitated by measuring the supernatant reverse transcriptase activity in exogenous reaction using poly(rC).oligo(dG) as template-primer. Two days after exposure, the synthetic glucocorticoid, dexamethasone (DXMT), increased spontaneous MuMTV production at optimal concentration (0.1 umol) up to 10x. Dibutyryl derivative of cyclic AMP had no effect on spontaneous MuMTV production, whereas the drug potentiated suboptimal concentrations of the glucocorticoid. Natural prostaglandins, potent agonists of adenylate cyclase catalyzing intracellular synthesis of cyclic AMP, enhanced both basal (up to 5x) and DXMT-stimulated (up to 1.6 times) MuMTV replication. The MuMTV-stimulating activity of prostaglandins decreased in the order of PGA1 greater than PGE1 greater than PGB1 greater than PGF2 alpha. Prostaglandins can be replaced partially by norepinephrine and isoproterenol by enhancing the DXMT-mediated MuMTV stimulation, whereas these drugs remained without effect on spontaneous MuMTV production. Theophylline, an antagonist of cAMP-phosphodiesterase converting cAMP to AMP, enhanced the virus-stimulating activity of DXMT as well as of prostaglandins. The enhancement of MuMTV production by adenylate cyclase agonists do not correlate absolutely with the estimates of intracellular cAMP levels, since the highest amounts of cAMP have been repeatedly observed in cells treated with PGE1 and norepinephrine. The results indicate that besides hormones, other hormone-like substances and cyclic nucleotides may be involved in the complex mechanism of hormone-regulated MuMTV genome expression. (Author abstract) (55 Refs)

27. HORMONE-DEPENDENT MATURATION OF MAJOR STRUCTURAL PROTEINS OF MURINE MAMMARY CANCER VIRUS.

Beriashvili MM, Chernova OB, Kolobkov SL, Kriukova IN
All-Union Cancer Res. Center, Moscow, USSR
Vopr Virusol; (1):34-38 1982

The effects of hormones on the processing of major structural proteins of murine mammary cancer virus (MMCV) were studied in virus-producing cells of mammary gland carcinoma of IK mice. Expression of the virus-specific products was assayed by radioimmunoprecipitation technique. Cells cultured in the hormone-free medium showed an expression of the products of gag and env genes. Incubation of cells with insulin and with dexamethasone resulted in marked stimulation of the processing of major glycoprotein of the virion envelope (gPr 70env). (10 Refs) (In RUS)

28. ERADICATION OF BOVINE LEUKEMIA VIRUS INFECTION FROM A HIGH-PREVALENCE HERD, USING RADIOIMMUNOASSAY FOR IDENTIFICATION OF INFECTED ANIMALS.

Ferrer JF
Section Viral Oncology, Comparative Leukemia Studies Unit, Sch. Veterinary Medicine, Univ. Pennsylvania, New Bolton Center, Kennett Square, PA, 19348
J Am Vet Med Assoc; 180(8):890-893 1982

Radioimmunoassay (RIA), using the virion glycoprotein antigen, was applied in an attempt to eradicate bovine leukemia virus (BLV) infection from a herd in which virtually all the adult cattle are infected. Considering that most calves born to BLV-infected cows are negative for BLV at birth and remain negative for the first several mo of life, the eradication program was based on the identification and isolation of the BLV-free calves born to infected cows. Twenty-five calves raised on colostrum and milk from their infected dams were classified as BLV-free on the basis of negative results in the RIA at 6 to 8 and 9 to 11 mo of age. These animals were maintained in either complete (10 calves) or partial (15 calves) isolation from infected cattle and were examined at regular intervals for BLV and BLV antibodies. With the exception of one calf in the group raised in partial isolation, the animals have remained free of BLV up to the time of the last evaluation, when they were 32 to 35 mo old. At these ages, more than 90% of the nonisolated cattle in the herd are BLV-positive. The data also show that this eradication trial would have failed if in the initial procedure used to classify the calves as BLV-free, the agar gel immunodiffusion test instead of the RIA had been used. Inasmuch as the 25 calves in this study were fed colostrum and milk from their dams, the fact that only 1 of the calves became infected during the 26 to 29 mo of observation provides further evidence that milk-borne transmission of BLV is infrequent and perhaps inconsequential. (Author abstract) (32 Refs)

29. HAEMAGGLUTINATION BY BOVINE LEUKAEMIA VIRUS.

Sentsui H, Thorn RM, Kono Y, Ferrer JF
Natl. Inst. Animal Health, Yatabe, Ibaraki 305, Japan
J Gen Virol; 59(part1):83-89 1982

Bovine leukemia virus (BLV) was found to agglutinate mouse erythrocytes. Under optimal conditions, including the use of neuraminidase-treated erythrocytes, 200 ug/ml of BLV purified from the supernatant fluid of BLV-infected bat cells had hemagglutinating titers of about 512 units. BLV hemagglutination was drastically affected by pH and temperature; maximum agglutination occurred at pH 6 and 4 C. That the BLV hemagglutinin is a glycoprotein was suggested by the fact that trypsin, potassium periodate or neuraminidase, but not lipid solvents or phospholipase C, significantly reduced the hemagglutinating (HA) activity of purified BLV. Furthermore, purified BLV glycoprotein of mol wt 51,000 (gp51) had HA activity. The receptors for BLV on mouse erythrocytes were inactivated by proteolytic enzymes but not by sodium deoxycholate or potassium periodate. Neuraminidase treatment of erythrocytes increased their agglutinability fourfold. Hemagglutination is a relatively sensitive test for detecting BLV glycoprotein because 0.4 ug/ml of glycoprotein can be detected by this method. The pH and temperature sensitivity of the BLV HA reaction and specificity for mouse erythrocytes distinguish BLV from that of equine infectious anemia virus and murine leukemia virus, the other C type retroviruses known to have HA activity. (Author abstract) (19 Refs)

GENETICS

30. ALLELISM AND LINKAGE STUDIES OF MURINE LEUKEMIA VIRUS ACTIVATION GENES IN LOW LEUKEMIC STRAINS OF MICE.

McCubrey J, Risser R
McArdle Lab. for Cancer Res., Univ. Wisconsin, Madison, WI, 53706
J Exp Med; 155(4):1233-1238 1982

Genes Inc-1 and Inb-1 that interact to enhance ecotropic murine leukemia virus induction in low virus strains of mice were previously found in BALB/c and C57BL/6 (B6) strains of mice, respectively, In order to relate these induction genes to known proviruses, their position in the mouse genome was determined. Classical genetic techniques to determine whether A/J, C3H/He, and SEC strains had a locus allelic to Inc-1 of BALB/c demonstrated that the Inc-1 loci in these mice were tightly linked. No recombinants were recovered in the 149 cultures examined, supporting the hypothesis that these genes are at identical locations in these strains. When B6 mice were mated to C57BR, and the F1 were crossed to BALB/c mice, it was shown that B6 and C57BR were allelic for Inb-1. The linkage of Inc-1 with Pgm-1 and Gus-1 was studied: Inc-1 was approx 24 centimorgans (cM) from Pgm-1 and was loosely linked to Gus-1. Inc-1 was on the centromeric side of Pgm-1. Analysis of the linkage of Es-1 to Inb-1 demonstrated that the loci were approx 30 cM apart. These data are consistent with two possible explanations: Inc-1 and Inb-1 are part of the virus-inducing genes Cv-1 and Bv-1, respectively, or Inc-1 and Inb-1 are tightly linked regulatory genes. (14 Refs)

31. FV-1 DETERMINANTS IN XENOTROPIC MURINE LEUKEMIA VIRUSES STUDIED WITH BIOLOGICAL ASSAY SYSTEMS: ISOLATION OF XENOTROPIC VIRUS WITH N-TROPIC FV-1 ACTIVITY IN THE CRYPTIC FORM.

Sakai K, Narita H, Adachi A, Tsuruta S, Yorifuji T, Ishimoto A
(c/o Ishimoto) Dept. Biophysics, Inst. Virus Res., Sakyo-ku, Kyoto 606, Japan
J Virol; 42(1):331-336 1982

By a biological assay system using phenotypically mixed ecotropic and xenotropic murine leukemia viruses, we investigated whether in the virions of a xenotropic virus there is N- or B-tropic Fv-1 determinant in active form. The existence of N-tropic Fv-1 determinant was demonstrated in SL-XT-1 xenotropic virus isolated from the spleen of a 3-mo-old SL mouse, and the N-tropic Fv-1 tropism was confirmed by analysis of the phenotypically mixed viruses harvested from clonal SC-1 cells doubly infected with the SL-XT-1 and B-tropic ecotropic viruses. However, neither N- nor B-tropic Fv-1 determinant was demonstrated in any xenotropic viruses isolated from embryo cells of BALB/c, NZB, or DBA/2 mice, or Cas E 1-IU, a xenotropic-like virus isolated from a wild mouse. (Author abstract) (19 Refs)

32. COMPLEMENTATION OF MAJOR HISTOCOMPATIBILITY HAPLOTYPES IN REGRESSION OF ROUS SARCOMA VIRUS-INDUCED TUMORS OF NONINBRED CHICKENS.

Brown DW, Collins WM, Ward PH, Briles WE
Dept. Animal Sciences, Univ. New Hampshire, Durham, NH, 03824
Poult Sci; 61(3):409-413 1982

Relative responses to Rous sarcoma virus (RSV)-induced tumors were studied in noninbred UNH 105 chickens. Chickens were blood typed for B alloantigens at 4 wk of age, and three homozygous genotyes (B23/B23, B24/B24, and B26/B26) and three heterozygous genotypes (B23/B24, B23/B26, and B24/B26) were studied. Chicks were inoculated with 0.1 ml of RSV (approx 20 pock-forming units) at 6 wk of age. A tumor profile index (TPI) was assigned to each chicken. Tumors developed in 795 chickens. Of B23/26 chickens, 54% were regressors compared with 34% of B23/B23 and 26% of B26/B26. The greatest incidence of tumor progression occurred in B24/B24 chickens (87%) in contrast to 23% in B23/B26 chickens. The homozygous genotypes had mean TPIs of 2.0-2.9 which were significantly different from each other. The greatest antitumor response was observed when the B23 and B26 haplotypes were combined; however, when B24 was combined with either B23 or B26, antitumor response was smaller than that observed for homozygotes of B23 or B26. The number and mean TPI of progeny from various kinds of matings were determined; the antitumor response of B23/B26 chickens was greater than that of the B23/B23 and B26/B26 chickens. These results suggest complementation of haplotypes influencing the anti-Rous sarcoma response. (19 Refs)

33. GENETIC INTERACTIONS BETWEEN TUMOR VIRUSES AND HOST CELLS.

Rowe WP
Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20205
Cancer; 49(10):1958-1962 1982

Accomplishments in the field of tumor virology over the past 25 yr are reviewed. The list of viruses known to cause tumors in nature or in laboratory systems has expanded greatly. The oncogenic viruses include retroviruses, herpesviruses, papovaviruses. Dramatic changes have taken place in the study of the genetic interactions between tumor viruses and virus-transformed cells, in searches for virus causation of tumors, and for a genetic and biochemical basis of malignant transformation. Polyoma viruses, adenoviruses, and retroviruses analyzed in mouse or hamster systems are discussed in relation to tumorigenesis. Infectious virus need not be present for tumor induction. Discoveries related to genetic interactions between viral and host cell genes in retrovirus leukemogenesis include the following: viruses produced directly from the inherited endogenous retroviral genes in the mouse are not tumorigenic; during the course of spreading infection, genetic recombinants arise between genomes of the infectious virus and the defective viral genes in the chromosomes of the host; a similar type of recombination can take place between infectious retroviruses and cellular genetic information; in B-lymphocytes transformed by avian retrovirus, only a piece of the virus genome may remain, analogous to the defective genome insertions seen with DNA tumor viruses. Other aspects of tumor virus DNA-host cellular DNA interactions are discussed. (49 Refs)

IMMUNOLOGICAL STUDIES

34. PROPERTIES OF MOUSE LEUKEMIA VIRUSES. XVIII. EFFECTIVE TREATMENT OF AKR LEUKEMIA WITH ANTIBODY TO GP71 ELIMINATES THE NEONATAL BURST OF ECOTROPIC AKR VIRUS PRODUCING CELLS.

Fischinger PJ, Dunlop NM, Schwarz H, Ihle JN, Weinhold K, Bolognesi DP, Schafer W
Virus Control Section, NCI, Frederick, MD, 21701
Virology; 119(1):68-81 1982

To suppress spontaneous leukemia, treatment of AKR mice with antibody to the murine leukemia virus (MuLV) major glycoprotein (gp71) must commence during a narrow 'window' period between birth and day 3. To examine the effect of treatment on virus expression, infectious MuLV cell centers (ICCs), free MuLV, and viral antigen presence were examined in various organs of control and antibody-treated neonatal AKR mice. The data graphically demonstrated that the treatment 'window' corresponded to a time just prior to the burst of ecotropic virus ICCs. The nature of ecotropic virus-positive cells and their elimination with treatment are discussed relative to later events in AKR leukemogenesis. (41 Refs)

35. IMPAIRMENT OF SPLENIC NATURAL KILLER CELL ACTIVITY OF MICE INFECTED WITH THE POLYCYTHEMIC STRAIN OF FRIEND LEUKEMIA VIRUS.

Migliorati G, Jezzi T, Favalli C, Garaci E, Rossi RB, Bonmassar E
Inst. Pharmacology, Univ. Perugia, via del Giochetto, I-06100 Perugia, Italy
Cancer Immunol Immunother; 12(2):177-179 1982

The effect of polycythemic strain Friend leukemia virus (FLV-P) infection on natural killer (NK) activity in FLV-P-susceptible DBA/2 inbred mouse recipients was examined. Spleen cells were collected from 4-wk-old control or FLV-P-infected donors on days 2, 7, 14, 21, and 28 after virus inoculation. Pools of four spleens each were tested for NK activity at various attacker:target ratios. A significant decrease of NK activity occurred as early as 7 days after infection. From day 14 onward, splenic NK function of infected mice was minimal. Moreover, an actual decrease of NK activity of the whole spleen occurred in these mice, as evidenced by the extremely low levels of lytic units per spleen detectable 3 wk after FLV-P infection. A limited but progressive decline of NK activity was found in the spleen of control non-infected donors, presumably expressing an age-dependent decrease of NK levels in the organ. The mechanism of suppression is discussed. It was suggested that suppression could be based on cell-mediated impairment of NK effector function, or on antigenic competition from splenocytes expressing NK antigens elicited by FLV-P. (19 Refs)

36. NATURAL ANTI-LYMPHOMA ACTIVITY IN C57BL/6 MICE: TIME COURSE OF APPEARANCE AND NATURE OF CYTOTOXIC ANTIBODIES.

Rubio N
Instituto de Immunologia y Biologia Microbiana, Velazquez 144, Madrid 6, Spain
Immunol Lett; 3(4):195-198 1981

The presence of cytotoxic antibodies in the sera of normal C57BL/6 mice was measured by the cytotoxicity test against syngeneic leukemic cells induced by endogenous radiation leukemia virus. Activity could be detected in sera from 5-14-mo-old mice. Study of the nature of the antibody response indicated the activity could be attributed mainly to IgM antibodies until the age of 10 mo, whereas in sera of 12-mo-old mice an increasing level of IgG-like antibodies was demonstrated. (16 Refs)

37. ROUS SARCOMA VIRUS-INDUCED TUMORS IN MICE - I. MACROPHAGE-MEDIATED NATURAL CYTOTOXICITY.

Giovarelli M, Landolfo S, Whitmore AC, Forni G
Dept. Microbiology, Univ. Torino, Via Santana 9, 10126 Torino, Italy
Eur J Cancer Clin Oncol; 18(3):307-315 1982

Lymphoid cells from normal untreated A.SW mice showed a cell-mediated cytotoxicity (CMC) towards Rous sarcoma virus-induced tumor lines in a 48-hr microcytotoxicity assay in vitro, using 3[H]-thymidine prelabeled tumor cells. The tissue distribution of this natural CMC shows high levels of activity in th peritoneal cavity, intermediate levels in bone marrow and spleen, and low levels in lymph node, peripheral blood and thymus. Natural CMC of unstimulated resident peritoneal cells against tumor cells was also found in several strains of mice. This was not dependent on the donor's age, since similar levels appeared in mice aged 1-40 wk. Passage through nylon wool columns or adherence to the plastic surface of resident peritoneal cells removed cytotoxic activity. By contrast, adherent cells displayed significant CMC levels. Treatment with carbonyl iron powder and magnet decreased peritoneal cell cytotoxicity when performed once and abolished it when repeated. All these results suggest that in mice, natural cytotoxicity against Rous sarcoma virus-induced tumors is primarily mediated by macrophages or macrophage-like cells. (Author abstract) (30 Refs)

38. DISSECTION OF THE ANTIGENIC DETERMINANTS EXPRESSED ON THE CELL SURFACE OF RSV-TRANSFORMED FIBROBLASTS BY MONOCLONAL ANTIBODIES.

Ferracini R, Prat M, Comoglio PM
Univ. Trieste, Sch. Medicine, Trieste, Italy
Int J Cancer; 29(4):477-481 1982

Fusion of P3/X63-Ag8 mouse myeloma cells with splenocytes obtained from mice hyperimmunized with a BHK hamster fibroblast line transformed by an env-strain of Rous sarcoma virus (RSV) resulted in the production of antibody-secreting hybridomas. Seven hybrid clones secreted antibodies binding to RSV-transformed BHK fibroblasts but not to the parental control non-transformed line. The antibodies produced by three of these clones did identify antigenic determinants expressed also on BHK cells transformed by SV40. The antibodies produced by four other clones reacted specifically with cells transformed by RSV but not with cells productively infected by the transformation-defective Rous-associated virus-I; one of these reacted with RSV-transformed hamster cells only, three others identified antigenic determinants common to RSV-transformed cells of different animal species. These data give further support to the idea that RSV-transformed cells express a cell-surface antigen, specific for transformation, the expression of which is controlled by the transforming src gene, and that the specificities carried on it follow a complex pattern, arising from the interaction between antigenic determinants of cellular and viral origin. (Author abstract) (49 Refs)

39. INCREASED OR DECREASED IMMUNOGENICITY OF TUMOR-ASSOCIATED ANTIGEN ACCORDING TO THE AMOUNT OF VIRUS-ASSOCIATED ANTIGEN IN RAT TUMOR CELLS INFECTED WITH FRIEND VIRUS.

Yamaguchi H, Moriuchi T, Hosokawa M, Kobayashi H
Lab. Pathology, Cancer Inst., Hokkaido Univ. Sch. Medicine, Kita-15, Nishi-7, Kita-ku, Sapporo 060, Japan
Cancer Immunol Immunother; 12(2):119-123 1982

Grading of tumor-associated antigen (TAA) is described with particular reference to the amount of virus-associated antigen (VAA) newly produced by non-lytic virus infection. Complement-dependent cytotoxic sensitivity of Friend virus (FV)-KMT-17 rat fibrosarcoma cells to anti-VAA serum increased proportionally following serial passage generations with a max at passage 6. The absorbing capacity potentials for removing 50% of anti-VAA serum activity were 12.0x higher in FV-KMT-17 (F6), and 3.2x higher in FV-KMT-17 (F4) cells than in FV-KMT-17 (F2) cells. No difference in absorbing capacities of FV-KMT-17 (F0, 2, 4, and 6) for anti-TAA serum were observed. When WKA/Hok rats were immunized with FV-KMT-17 (F2, 4, 6 and 0) cells having various amounts of VAA and subsequently challenged with 10(5) or 10(6) viable KMT-17 cells, survival rates of 20.8%, 83.3%, 18.2% and 45.8%,respectively, were obtained. Immunization of FV-tolerant rats with FV-KMT-17 (F2, 4, and 6) cells resulted in similar levels of transplantation resistance without marked difference from the non-passage F0. Immunization of normal rats with a mixture of WLFT-6 rat thymoma cells [1.6 x 10(7) possessing an amount of VAA almost equivalent to that in FV-KMT-17 (F4)] and 5.0 x 10(7) KMT-17 cells resulted in lower transplantation resistance than for FV-KMT-17 (F4) cells alone, suggesting that VAA and TAA must be present on the same cell. The results indicated that TAA immunogenicity increases when an appropriate amount of VAA is expressed on the tumor cell surface and decreases when a relatively low or excessive amount of VAA is expressed. (22 Refs)

40. INFLUENCE OF SELECTIVE ABSENCE OF H-2KKAPPA ON GROSS VIRUS LEUKAEMIAS IN VITRO AND THE IMPLICATIONS FOR IN VIVO SURVEILLANCE OF LEUKAEMIA.

Festenstein H, Schmidt W, Alonzo A, Leben L
Dept. Immunology, London Hosp. Medical Coll., London, England
Protides Biol Fluid Proc Colloq; 29:231-235 1982

Results are presented of direct complement dependent cytotoxicity tests using anti H-2Kkappa (H-2Kk) monoclonal antibody on five primary AKR leukemias. These and earlier results permit the conclusion that the absence/reduction of the H-Kk gene product is not uncommon in Gross virus leukemia. In search of the biological implication of this finding, a comparison was made of the ability of the K-GV BALB/c Gross virus tumor, which lacks Kk, and other Gross virus tumors with normal H-2Kk representation, to act as targets in cell mediated lympholysis (CML). Results showed that resistance to syngeneic CML is apparently due to the absence of Kk and is thus a failure of associative recognition. Results suggest a new mechanism of escape of T cell surveillance by leukemic cells which involves selective decrease of the H-2Kk antigens, which in this and other studies, have been shown to serve as elements of associative recognition in Gross virus leukemia. (6 Refs)

41. GENETIC CONTROL OF ANTIBODY RESPONSES TO MOLONEY VIRUS IN RATS.

Jones JM, Gunther E, Soderberg FB
Dept. Pathology, Univ. Arkansas for Medical Sciences, Little Rock, AR, 72205
Leuk Res; 6(1):127-129 1982

Antibody responses to Moloney leukemia virus (M-MuLV) of various strains of rats were examined to determine the role of the major histocompatibility complex (RT1) in generating them. All animals were immunized with three injections of 100 ug M-MuLV. F2 animals of BN (n/n: high responder) and LEW (l/l: low responder) crosses did not show differences in response to M-MuLV p30, which were intermediate. LEW-1N animals, which have the BN high response RT1n gene bred onto a LEW background, gave very low antibody responses to p30, p15, and gp70. Antibody responses of BN-Lrl congenic rats, which have the LEW high response gene to phytohemagglutinin bred onto the BN background, gave responses slightly but not significantly lower to p30 and gp70, as compared to BN rats. Even though studies with F2 hybrids suggest that RT1 may have more effect on response to gp70 than to p30, it appears that non-RT1 genes are important for high antibody responses to M-MuLV because the LEW-1N rats with a high responder RT1n of BN haplotype on a LEW background were low responders. (10 Refs)

42. THE BIOLOGY OF MARROW DEPENDENT CELLS IN MICE.

Kumar V, Bennett M
Dept. Pathology, Boston Univ. Sch. Medicine, Boston, MA, 02118
The Handbook of Cancer Immunology Volume 6: Lymphoid Cell Subpopulations-Structure, Function, and Interactions. Waters H, ed. New York, Garland STPM Press, 314 pp., 1981.

After 89Sr administration in mice, certain effector functions such as marrow allograft reactivity, genetic resistance against Friend virus leukemia, and natural killer (NK) activity are lost. Such effector functions may be mediated by a distinct class of immunocompetent cells which are critically dependent on the bone marrow microenvironment (M cells) for differentiation. These M cells may be NK cells. The relationship between NK cells and other effector functions of M cells, and the regulatory function of M cells, are discussed. (41 Refs)

OTHER RELATED STUDIES

43. COMPARATIVE UPTAKE OF ADRIAMYCIN AND DAUNORUBICIN IN SENSITIVE AND RESISTANT FRIEND LEUKEMIA CELLS MEASURED BY FLOW CYTOMETRY.

Tapiero H, Fourcade A, Vaigot P, Farhi JJ
Departement de Pharmacologie Cellulaire et Moleculaire, Unite Simone et Cino Del Duca de Pharmacologie Humaine de Cancers, Institut de Cancerologie et d'Immunogenetique (INSERM U-50), Hopital Paul-Brousse, 14, avenue Paul Vaillant Couturier, 94804-Villejuif, France
Cytometry; 2(5):298-302 1982

The fluorescent intensity of adriamycin (ADM) and daunorubicin (DNR) on a single cell level was studied in sensitive and resistant Friend leukemia cells (FLC) derived from a clone of Friend virus transformed cells 745A. The uptake of ADM and DNR in FLC was analyzed by incubating 10(7) cells in a growth medium containing increasing amounts of ADM or DNR. The spontaneous fluorescence of untreated cells showed a single narrow peak whose position varied with the sensitivity of measurements. The fluorescence intensity was related to the drug concentration. Distribution profiles resulting from the exposure of FLC to 0, 1, 3, 10, and 30 ug ADM/ml are presented. When cells were incubated under the same conditions with DNR, higher fluorescence values were observed. The exposure of cells to ADM and to DNR in the presence of sodium azide (2 x 10(-2) M) did not affect the distribution of fluorescence peaks. Distribution of peaks changed after incubation at 37 C, 20 C, or 4 C. Incorporation into isolated nuclei was not affected by low temperature. Sublines of FLC resistant to ADM and DNR were obtained by continuous exposure to increasing concentrations of each drug over a period of 9 mo and maintained at 1 ug/ml of ADM and DNR for 3 mo. Cross resistance between these two sublines was observed. Exposure of these sublines to ADM and DNR showed that the mean cellular fluorescence was related to the initial concentration of drugs but at lower values than in sensitive cells. Resistant cells exposed to 10 ug DNR/ml led to a heterogeneous fluorescence distribution as compared to ADM exposed cells. (30 Refs)

44. HYPERTHERMIA IN CANCER THERAPY: POTENTIAL APPLICATION TO BRAIN TUMORS.

Tanaka R
Dept. Neurosurgery, Brain Res. Inst., Niigata Univ., Niigats, Japan
No Shinkei Geka; 10(1):7-19 1982

Concepts involved in the application of hyperthermia to cancer therapy were introduced, and problems with hyperthermia and its future development as a method for treatment of tumors were discussed. Basic biological studies of hyperthermia indicate that hyperthermia affects tumor tissues because of the following reasons: selective sensitivity of tumor cells to heat, which influences respiration and glycolysis, synthesis of nucleic acids and proteins, and lysosomes; immediate cell killing; and delayed cell killing. Using rats bearing Rous sarcoma virus-induced brain tumors and monkeys with primary brain tumors, radiofrequency hyperthermia (13.56 megaH) produced marked antitumor effects. Since the tumor cell:normal surrounding cell temperature difference was as high as 8-10 C, it was thought that hyperthermia as high as 48-50 C would be attainable in the brain (due to cerebral blood flow, the brain maintains a steady temperature of 40 C). Compared to the use of radiotherapy or chemotherapy alone, combinations of hyperthermia and 60Co radiotherapy or of hyperthermia and chemotherapy prolonged the growth times of tumors, suggesting possible combinations of therapies that might be effective in clinical settings. With advances in hyperthermia apparatuses, treatment of brain tumors with hyperthermia was thought to be possible in the future. (90 Refs) (In JPN)

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VIRUS ISOLATION AND CHARACTERIZATION

1. ASYMPTOMATIC TYPE C VIRUS CARRIERS IN THE FAMILY OF AN ADULT T CELL LEUKEMIA PATIENT.

Miyoshi I, Taguchi H, Fujishita M, Niiya K, Kitagawa T, Ohtsuki Y, Akagi T

Dept. Medicine, Kochi Medical Sch., Oko-cho, Nankoku-shi, Kochi-ken 781-51, Japan

Gan; 73(2):339-340 1982

Serologic and virologic studies were performed in 14 members of the family of a 49-yr-old male patient with adult T cell leukemia (ATL). The patient and family lived in Kochi, an area where the incidence of ATL appears to be relatively high. ATL antigens (ATLA) and Type C virus particles were detected in short-term cultures of peripheral lymphocytes from 4/5 family members who were ATLA antibody positive. The five ATLA antibody positive family members were all asymptomatic and hematologically normal except for one member, in whom a persistent leukocytosis with several percent abnormal lymphocytes had been observed for two yr. It was not yet de-

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termined whether vertical or horizontal infection was involved in the virus transmission in this family. (5 Refs)

2. A RETROVIRUS ASSOCIATED WITH HUMAN ADULT T CELL LEUKEMIA: IN VITRO ACTIVATION.

Hinuma Y, Gotoh Y, Sugamura K, Nagata K, Goto T, Nakai M, Kamada N, Matsumoto T, Kinoshita K
Inst. Viral Res., Kyoto Univ., Shogoin Kawahara-machi, Sakyo-ku, Kyoto 606, Japan
Gan; 73(2):341-344 1982

Presence of adult T cell leukemia antigen (ATLA) was studied in the mononuclear cell fractions of peripheral blood derived from 11 patients (9 men, 2 women; 48-83 yr old) with adult T cell leukemia (ATL), from a 54-yr-old man with mycosis fungoides (MF), and from 8 healthy adults (6 men, 2 women; 21-44 yr old). The mononuclear cell fractions were cultured in the presence and/or absence of interleukin-2 (IL-2) or T cell growth factor. Some of the fractions were also examined with electron microscopy for virus particles. ATLA positive cells were not detected in any of the cell preparations examined prior to culturing. However, ATLA-bearing cells were observed in the cultures from 6/11 ATL patients and 1/2 ATLA antibody-positive healthy subjects. No ATLA-bearing cells were detected in cultures of one patient with MF and six ATLA antibody-negative healthy subjects. High percentages of ATLA positive cells were found 2-3 days after starting cultures without IL-2; the ATLA were located in the cytoplasm of rather small leukemic cells and were often aggregated. The ATLA-bearing cells in cultures supplemented with IL-2 for a greater than 2 wk were large and often multinuclear with blastoid morphology. Presence of Type C virus particles was observed with electron microscopy in ATL-derived cultures with a high percentage of ATLA positive cells. The results showed that (1) peripheral blood cells of many patients with ATL contain sufficient information for ATLA or ATL virus (ATLV) formation in a repressed form, and suggest that (2) ATLA is associated with ATLV and (3) ATLV is present not only in ATL patients but also in anti-ATLA positive healthy individuals. (6 Refs)

3. SERO-EPIDEMIOLOGIC STUDIES ASSOCIATE THE HUMAN T-CELL LEUKEMIA-LYMPHOMA VIRUS (HTLV) WITH ADULT MALIGNANCY OF MATURE T-CELLS (MEETING ABSTRACT)

Robert-Guroff M, Kalyanaraman VS, Sliski A, Blattner W, Catovsky D, Sarngadharan MG, Gallo RC
Litton Bionetics, Inc., Kensington, MD, 20895
Fed Proc; 41(3):689 1982

HTLV, a unique human retrovirus (RNA tumor virus), was isolated from cells of patients with lymphomas and leukemias of mature T-cells. Surveys of sera for antibodies to HTLV have shown HTLV to be rarely associated with such diseases in the US, but strongly linked to Japanese adult T-cell leukemia (ATL), lymphosarcoma T-cell leukemia (LCL), and peripheral T-cell lymphoma. LCL is a malignancy of mature T-cells seen in some Caribbeans. ATL is a similar disease clustered geographically in Southwest Japan. Sera of 19 of 22 ATL patients and 3 of 3 LCL patients had antibodies to HTLV p24 and p19 as determined by radioimmunoprecipitation of p24 or by competition radioimmunoassay with a monoclonal anti-p19. Among sera of relatives of sero-positive patients, 20% were also positive, supporting the infectious nature of HTLV. Other normal donors lacked antibodies to HTLV, except for some healthy Japanese in the ATL endemic area, suggesting widespread viral exposure. Sera of children in the US with leukemias, lymphomas, and solid tumors were negative, as were sera from numerous adults with various neoplasias. While HTLV is thus not prevalent in this country, it may play a role in the etiology of mature T-cell neoplasias in other geographic locales. (no Refs)

4. EFFECTS OF ESTRAMUSTINE AND MEGESTROL ON ULTRASTRUCTURE OF RAT VENTRAL PROSTATE.

Dinchuk JE, Chai LS, Karr JP, Murphy GP, Sandberg AA
Dept. Experimental Surgery, Genetics, Endocrinology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Urology; 19(5):511-522 1982

The effects of estramustine phosphate on the ultrastructure of the rat ventral prostate closely resemble postcastration events, ie, a decrease in cell size and secretory activities. The fibromuscular stroma, especially collagen fibers, appear to lose their adherence to adjoining muscle cells and fibroblasts. An infiltration of lymphocytes was noted in dilated regions of the fibromuscular stroma. There was an increase in cellular activity in the ventral prostate of rats treated with megestrol acetate with varying degrees of cellular atrophy and cytoplasmic disorganization. Squamous metaplasia was evident in one experimental group of MA-treated animals. Particles resembling mature C-type were observed in several prostates from control and experimental animals. (Author abstract) (46 Refs)

VIRUS ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

5. TWO RETROVIRUSES WITH SIMILAR TRANSFORMING GENES EXHIBIT DIFFERENCES IN TRANSFORMING POTENTIAL.

Linial M
Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
Virology; 119(2):382-391 1982

The genomes of MH2 and MC29 have been shown to be highly similar and contain the same oncogenic sequence termed myc. Both viruses can transform Japanese quail (Coturnix coturnix japonica) embryo fibroblasts and mature peripheral blood macrophages in vitro. However, a striking difference is observed after in vivo infection of 3-wk-old quail. Neither virus causes either sarcomas or myelocytomas. MC29 is only weakly oncogenic; only 2 of 29 birds developed tumors which were localized in the liver. In contrast MH2 is highly oncogenic; birds generally developed solid tumors near the site of injection, or liver tumors. When the solid tumors were placed in culture they gave rise to transformed macrophages, and surprisingly, erythrocyte-like cells, which were not transformed. MH2 and MC29 also exhibited different efficiencies of macrophage and fibroblast transformation in vitro. It is postulated that the biological differences between the two viruses could be related to differences in processing of myc sequences. (Author abstract) (22 Refs)

6. CARCINOGEN- AND RADIATION-TRANSFORMED C3H 10T1/2 CELLS CONTAIN RNAS HOMOLOGOUS TO THE LONG TERMINAL REPEAT SEQUENCE OF A MURINE LEUKEMIA VIRUS.

Kirschmeier P, Gattoni-Celli S, Dina D, Weinstein IB
Cancer Center/Inst. Cancer Res., Div. Environmental Science, Columbia Univ., New York, NY, 10032
Proc Natl Acad Sci USA; 79(9):2773-2777 1982

Carcinogen- or radiation-transformed C3H 10T1/2 murine fibroblasts transcribe a set of poly(A)+ RNAs that contain sequences homologous to the long terminal repeat (LTR) sequence of Moloney murine sarcoma virus. These LTR-containing RNAs consist of a series of discrete bands ranging in size from about 38 to 18 S. The higher mol wt molecules (30-38 S) in this set of RNAs also contain sequences homologous to the gag, pol, and env genes of a murine leukemia virus. A 24S RNA contains sequences homologous to the env gene of murine leukemia virus. A 20S and an 18S RNA also share homology with the LTR probe but fail to hybridize to the gag, pol, or env probes or to a probe for the U3 region of the LTR sequence. Thus, the latter transcripts do not appear to arise from a known endogenous murine leukemia virus genome. Although this entire set of RNAs is absent from normal C3H 10T1/2 cells (or is present at an extremely low level), these RNAs are induced by BrdUrd or 5-azacytidine. The presence of these RNAs may provide highly sensitive molecular markers of transformation of mouse cells. (Author abstract) (35 Refs)

7. RAPID THYMOMAS INDUCED BY ABELSON MURINE LEUKEMIA VIRUS.

Cook WD
Walter and Eliza Hall Inst. Medical Res., P.O. Royal Melbourne Hosp., Victoria, 3050, Australia
Proc Natl Acad Sci USA; 79(9):2917-2921 1982

Abelson murine leukemia virus (A-MuLV) is derived from the thymotropic Moloney leukemia virus. However, injection of mice with A-MuLV conventional routes results in rapidly arising peripheral and bone marrow lymphomas, not thymomas or T cell tumors. In this study thymomas have been induced by intrathymic injection of A-MuLV into BALB/c and C57BL/Ka mice. In both strains thymomas arose with short latent periods, comparable with the latencies of nonthymic tumors induced by intraperitoneal injection of A-MuLV and significantly shorter than those of thymomas induced by intrathymic injection of Moloney leukemia virus. Cells of the BALB/c thymomas were predominantly Thy-1-; those of C57BL/Ka thymomas were predominantly Thy-1+. Tissue culture lines were established and cloned. Some of these expressed low amounts of Thy-1 and one also expressed Lyt-1. Virus from cloned lines transformed 3T3 cells in vitro and induced Abelson disease in vivo when injected intraperitoneally into neonates. The A-MuLV p120 protein has been precipitated from metabolically labeled cell lysates of one cloned Thy-1+ line. These results show that A-MuLV can transform cells in the T-lymphocyte lineage. (Author abstract) (22 Refs)

8. TRANSFORMATION INDUCED BY ABELSON MURINE LEUKEMIA VIRUS INVOLVES PRODUCTION OF A POLYPEPTIDE GROWTH FACTOR.

Twardzik DR, Todaro GJ, Marquardt H, Reynolds FH, Stephenson JR
Lab. Viral Carcinogenesis, NCI, Frederick, MD, 21701
Science; 216(4548):894-897 1982

Rat embryo fibroblast transformed by Abelson murine leukemia virus (MuLV) produce and release a transforming growth factor (TGF). Production of this factor is correlated with a tyrosine-specific protein kinase that is functionally active and is associated with the major Abelson MuLV gene product, P120. Transformation-defective mutants of Abelson MuLV do not transform cells, do not have their virus coded transforming gene product phosphorylated in tyrosine, and do not induce TGF production. Abelson MuLV-induced TGF morphologically transforms cells in culture, competes with 125I-labeled epidermal growth factor (EGF) for binding to cell receptors, and induces phosphorylation of tyrosine acceptor sites in the 160,000-dalton EGF membrane receptor. After purification to homogeneity, Abelson virus-induced TGF migrates as a single polypeptide with an apparent size of 7,400 daltons as determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. (Author abstract) (27 Refs)

9. INDUCTION OF SARCOMAS IN ATHYMIC MICE.

Beattie GM, Knowles AF, Jensen FC, Baird SM, Kaplan NO
Cancer Center, Univ. California San Diego, La Jolla, CA, 92093
Proc Natl Acad Sci USA; 79(9):3033-3036 1982

During the course of serial passage of 50 human xenografts in the athymic mouse over a period of 5 yr we have observed two cases of induction of sarcomas in the murine stromal tissue associated with the human xenografts. Both times the growth of the murine sarcomas overtook that of the human xenograft. This change was monitored by analysis of the lactate dehydrogenase isozyme profile and histology of each passage of the human xenografts in the athymic mice. The two murine sarcomas were subsequently established in tissue culture. The sarcoma cell lines were found to be malignant by morphological and growth characteristics and were tumorigenic. They contained large amounts of murine leukemia virus when assayed for reverse transcriptase activity by infection of mouse SC-1 cells and BALB/c and NIH Swiss fibroblasts with filtered supernates, and some type C virus particles were observed by electron microscopy in tumor tissues. However, we were unable to demonstrate the presence of murine sarcoma virus by in vitro transformation of fibroblasts or sarcoma formation in vivo with cell free filtrates. Preliminary biochemical data indicate that the sarcomas are extremely high in plasma membrane ATP phosphohydrolase. (Author abstract) (16 Refs)

10. THE CLONALITY OF ROUS SARCOMAS (MEETING ABSTRACT)

Cutting JA, Chalmers JH, Strebel FR, Watanabe DH, McBride RA
Department of Pathology, Baylor College of Medicine, Houston, TX, 77030
Fed Proc; 41(3):689 1982

Using molecular hybridization, others have shown that in the chicken, leukemic cells of ALV (avian leukosis virus)-induced leukosis are monoclonal. We wished to enquire if the solid sarcomas caused by the related avian sarcoma viruses are also monoclonal. Following wingweb inoculation with Schmidt-Ruppin RSV-B (Rous sarcoma virus) we at first observe discrete foci (papillae) of cell proliferation. With growth, these usually fuse to form a single sarcoma. There is proportionality of the papillae number over 3 log 10 dilutions of the inoculum. For a fixed inoculum the papillar number is different in three inbred lines of chickens (G-B1, G-B2 and G-B3). For each line there is concordance between the in vivo papillae number and the in vitro ffu. With limiting inocula there is less than 100% tumorigenesis, and, for the mean number of papillae (all birds), the Poisson probability for at least one papilla/bird equals the fraction of birds developing sarcomas. These observations indicate that each papilla develops from an infected focus generated at inoculation and that each is competent for sarcoma development. Since a sarcoma can be formed by papillar fusion it is potentially polyclonal. We are analyzing restriction fragments of DNA from papillae and emergent sarcomas with an ALV probe, to determine if the RSV genome integrates at different sites. (no Refs)

11. IN VIVO STUDIES ON HEMOPOIETIC STEM CELLS AND TARGET CELLS FOR FRIEND VIRUS INFECTION IN VITRO.

Seidel HJ, Kreja L

Dept. Clinical Physiology, Univ. Ulm, Oberer Eselberg, D-7900 Ulm, W. Germany

Exp Hematol; 10(5):459-466 1982

Friend virus replicating target cells have been characterized by in vitro infection of bone marrow cells from DBA/2 mice after multiple injections of hydroxyurea (HU), after bleeding and/or hypertransfusion and after busulfan treatment. The concentration of CFUS, BFUE and CFUE in the cell suspension was correlated with the number of infectious centers (IC) induced after infection. HU treated mice were also infected in vivo. The results demonstrate that there is almost no target cell 4 hr after the last of 4 HU injections. The number of IC induced could correlate with the numbers of CFUS in the HU experiment, but this possibility can be rejected based on the busulfan experiments. All results, including those after bleeding and/or hypertransfusion are compatible with a target cell between BFUE and CFUE, as suggested by other in vitro infection methods and also in vivo experiments. (Author abstract) (28 Refs)

12. A STUDY OF ADDED GM-CSF INDEPENDENT GRANULOCYTE AND MACROPHAGE PRECURSORS IN MOUSE SPLEEN INFECTED WITH MYELOPROLIFERATIVE SARCOMA VIRUS (MPSV).

Klein B, Le Bousse-Kerdiles C, Smadja-Joffe F, Pragnell I, Ostertag W, Jasmin C

Centre Paul Lamarque, Hopital Saint Eloi, BP 5054, 34033 Montpellier, France

Exp Hematol; 10(4):373-382 1982

A subpopulation of granulocyte and macrophage precursors (GM-CFUc) differentiating in the agar colony technique of Bradley and Metcalf into mature granulocytes and macrophages, without the addition of granulocyte and macrophage colony stimulating factor (GM-CSF), can be detected in MPSV infected mice These precursors were detected 5 days after virus infection, reaching a maximal concentration of 1/10,000 spleen or bone marrow cells, 25 days after viral infection. The number of the added GM-CSF independent GM-CFUc was linearly correlated with the number of seeded MPSV hematopoietic cells. No GM-CSF producing cells could be detected in the MPSV spleen using normal bone marrow GM-CFUc as responder cells. Study of the GM-CSF sensitivity of the GM precursors has demonstrated the existence of two GM-CFUc populations in the MPSV spleen: (a) a GM-CSF dependent population with a GM-CSF sensitivity similar to that of normal GM-CFUc, (b) a GM-CFUc population which differentiated in the absence of detectable amount of GM-CSF and of which differentiation was not affected by the addition of progressive amounts of GM-CSF. A possible model explaining these results is proposed. (Author abstract) (23 Refs)

13. IN VITRO TRANSFORMATION BY AVIAN ERYTHROBLASTOSIS VIRUS RECRUITS CELLS OF ERYTHROID LINEAGE WITH VARYING DEGREE OF DIFFERENTIATION.

Therwath A, Scherrer K

Dept. Microbiology, Biomedical Center, Box 581, S-751 23 Uppsala, Sweden

Int J Cancer; 29(5):555-558 1982

We have previously shown that the AEV infection of leukosis-free chickens provokes an erythroleukemia in the infected birds, and that the target cell for virus transformation is most likely an early pro-erythroblast comparable to the BFU-E. The virus infection correlates with a block in differentiation which was studied at a specific cellular gene level, namely that of the globin genes. In live birds, the viral transformation has been found to affect the transcriptional activity of two out of three adult globin genes and the phenotypic expression of the third. Indeed, the alphaa gene that is transcribed is silent as well, since its transcription product is fully eliminated in the nucleus following an 'abortive processing'. Chick bone marrow cells can also be transformed in vitro by AEV in which case the virus recruits, as targets, cells of the erythroid lineage belonging to a wider spectrum and hence in varying degrees of differentiation. In contrast to the results obtained with in vivo transformed cells, molecular hybridization with globin cDNA probes showed that in the erythroblasts transformed in vitro under tissue culture conditions all the three adult globin genes are transcriptionally active. Judging from our present results, we may propose that AEV transformation in vitro does not shut off but only modulates the already functioning erythroid cell differentiation program. (14 Refs)

14. PROTHYMOCYTES IN LONG TERM BONE MARROW CULTURES DERIVED FROM PRELEUKEMIC AKR MICE (MEETING ABSTRACT)

Zielirski C, Waksal SD

Tufts Cancer Research Center, Boston, MA, 02111

Fed Proc; 41(3):608 1982

Long term bone marrow (Dexter) cultures were used to study preleukemic changes during spontaneous leukemia in AKR mice. Bone marrow cells derived from AKR and control mice which were 6-8, 14-16 and greater than 24 weeks of age were grown in long term in vitro culture for up to 8 months. Cultures were analyzed for virus content as well as expression of differentiation antigens. High levels of ecotropic virus were expressed in all AKR bone marrow cultures. Low levels of xenotropic virus were found in cultures derived from AKR mice greater than 24 weeks of age. No polytropic virus could be detected. These cultures contained prothymocytes which could repopulate irradiated AKR and F1 recipients. No leukemic cells could be detected in bone marrow cultures with AKR cells. These studies show normal lymphopoiesis in long term bone marrow cultures of AKR mice and suggest that leukemogenic changes occur only after thymic repopulation. (no Refs)

15. IDENTIFICATION OF PLAQUE ISOLATES OF AN AVIAN RETROVIRUS CAUSING RAPID AND SLOW ONSET OSTEOPETROSIS.

Smith RE, Morgan JH

Dept. Microbiology and Immunology, Duke Univ. Medical Center, Durham, NC, 22710

Virology; 119(2):488-499 1982

This study examines the basis for the observation that serum stocks of myeloblastosis-associated virus MAV-2(0) obtained from chickens with osteopetrosis induced abnormal bone growth after a latent period of less than 3 wk, while stocks of plaque-purified MAV-2(0) induced abnormal bone growth only after latent periods of 6 wk or greater. To establish the basis for this distinction, 85 plaque isolates were derived from a serum stock of MAV-2(0), and each plaque isolate was injected into 10-day-old chick embryos. Infected chicks were examined 3 wk after hatch for the wt of their body, bursa, and bone. Three MAV-2(0) plaque isolates caused bone growth that was at least five fold greater in infected than in uninfected animals. The other 82 plaque isolates caused slight osteopetrosis or none at all. The serum stock of MAV-2(0) therefore consisted of two forms of virus: one caused rapid onset osteopetrosis, and the other caused slow onset osteopetrosis. Almost all plaque isolates of MAV-2(0) caused decreased body and bursa weights, but with the rapid onset plaque isolates, these effects were more severe. The ability to cause rapid onset osteopetrosis was stable for three sequential plaque purifications. RNA from rapid and slow MAV-2(0) plaque isolates did not differ in T1 oligonucleotide fingerprints, and all had RNA 8.2 Kb in length. Structural polypeptide compositions of rapid and slow plaque isolates were essentially the same, as defined by migration on SDS-polyacrylamide gels. The growth rate of the isolates on embryonic limb bud cells and chick embryo fibroblasts were similar. (Author abstract) (31 Refs)

16. ORGANOTROPISM OF THE LYMPHOPROLIFERATIVE DISEASE VIRUS (LPDV) OF TURKEYS.

Gazit A, Schwarzbard Z, Yaniv A, Ianconescu M, Perk K, Zimber A

Dept. Human Microbiology, Sackler Sch. Medicine, Tel-Aviv Univ., Tel-Aviv, Israel

Int J Cancer; 29(5):599-604 1982

Turkey poults were inoculated with lymphoproliferative disease virus (LPDV) of turkey, and the organotropism of the inoculated virus was determined from the kinetics of virus expression and tumor formation. Molecular hybridization experiments, conducted to determine the level of viral RNA expression in the various organs of infected birds, established lymphoid tissues, including bone marrow, as the target for LPDV infection. Of these, bone marrow was the first to be infected but subsequently virus replication extended to the thymus, the spleen and the bursa of Fabricius. The low level of LPDV expression in non-target organs probably stemmed from infiltration of infected lymphatic cells. The fact that the main organs for virus replication were not invariably the ones most clinically involved suggests that the target cells for virus infection need not necessarily be the targets for virus oncogenicity. A possible mode for LPDV infection and transformation is proposed. (Author abstract) (23 Refs)

17. ULTRASTRUCTURE OF THE CYCLING UTERUS IN A HIGH MAMMARY TUMOR AND A LOW MAMMARY TUMOR STRAIN OF MOUSE (MEETING ABSTRACT)

Brophy MO, Spring-Mills E

Department of Anatomy, Upstate Medical Center, Syracuse, NY

Anat Rec; 202(3):22A 1982

The mammary gland in the low tumor strain of mouse, C3HeB/FeJ, displays a more consistent and regular pattern of branching at all stages of development than the mammary gland of the high tumor strain of mouse, C3H/HeJ. The high tumor mouse infects its young with the mouse mammary tumor virus (MMTV) via its milk; the low tumor strain does not. The MMTV can be identified in electron micrographs of the mammary epithelium of infected animals. In order to test whether the differences in mammary gland structure between the high tumor and the low tumor strain of mouse were due to a direct effect of the viral particles in the epithelial cells or to a generalized effect of the virus on the hormonal milieu, we compared the uterine morphology in these two strains of mice. Vaginal smears were made and the mammary glands, ovaries, oviducts and uterus from 26 C3H/HeJ and 34 C3HeB/FeJ mice, aged 8 to 20 weeks, were prepared for light and electron microscopy. Preliminary evidence indicates that the eosinophilic band which is apparent in the apical cytoplasm of the uterine epithelial cell in late diestrus and proestrus with the light microscope is composed of many small empty vesicles located just beneath the lumenal surface. By the end of metestrus II, the vacuoles are decreasing in number and size, and contain less material. Although the estrus cycle pattern is similar in both the high and low tumor strain of mouse, the uterine ranges are more consistent and regular in the low tumor strain of mouse. (no Refs)

18. BIOLOGICAL CONTROL OF THE PRENEOPLASTIC STATE IN MAMMARY CANCER (MEETING ABSTRACT)

Medina D

Department of Biology, Baylor College of Medicine, Houston, TX

Control of Human Cancer III, March 6-7, 1981, Fort Lauderdale, Florida. North Ridge General Hospital 19 pp., 1982.

The concept of mammary preneoplasia developed in the mouse model had been successfully applied to both chemical carcinogen induced mammary cancer in the rat and human breast cancer. The mouse model still remains the most accessible system for experimental analysis of the biological factors which regulate the preneoplastic state. The initiated cells which possess a high risk for generating neoplastic cell variants. Oncogenic agents, such as mammary tumor viruses and chemical carcinogens, induce preneoplastic cells and enhance the rate at which neoplastic cell variants arise from preneoplastic cell populations. Preneoplastic cells can be interpreted as initiated cells, analagous to such cells in epidermal carcinogenesis systems. Substrate interactions and local cellular interactions play a significant role in the expression of both preneoplastic and neoplastic cells. Data will be discussed which supports the hypothesis that preneoplastic cells are initiated soon after interaction between an oncogen and normal mammary cells. The long latent period between initiation and expression of preneoplastic cells is modulated by hormones, diet, local cellular interactions, and other promoting agents. (no Refs)

19. CRANIAL NEURAL CREST CELLS: INHIBITION OF DIFFERENTIATION IN CULTURE.

Greenberg JH, Glimelius B, Knudson
Lab. Developmental Biology and Anomalies, Natl. Inst. Dental Res., NIH, Bethesda, MD, 20205
Adv Neurol; 29:105-113 1981

The effects of dimethylsulfoxide, 5-bromo-2'-deoxyuridine, retinoic acid, infection with Rous sarcoma virus, and temperature on differentiation of cultured chick neural crest cells are described. Exogenous agents that interfere with neural crest cell differentiation may act at a variety of sites, and may sometimes mimic genetic or environmental influences that occur in vivo and lead to birth defects. (25 Refs)

20. TRANSFORMATION BY AVIAN SARCOMA VIRUSES LEADS TO PHOSPHORYLATION OF MULTIPLE CELLULAR PROTEINS ON TYROSINE RESIDUES.

Beemon K, Ryden T, McNelly EA
Dept. Biology, Johns Hopkins Univ., Baltimore, MD, 21218
J Virol; 42(2):742-747 1982

Phosphoamino acid compositions were determined for 10 size classes of cellular proteins, separated by electrophoresis through one-dimensional sodium dodecyl sulfate-polyacrylamide gels. Phosphotyrosine-containing proteins were observed in uninfected chicken embryo fibroblasts in every size class analyzed, ranging from approx 20,000 to greater than 200,000 daltons. Transformation of chicken embryo fibroblasts by Rous sarcoma virus or PRC II avian sarcoma virus led to increases in phosphorylation of proteins at tyrosine residues in all of these size classes. A large fraction of the phosphotyrosine-containing protein molecules observed in Rous sarcoma virus-transformed cells was larger than 100,000 daltons with a second broad peak in the 35,000-to 60,000-dalton range. This study suggests that there are a number of substrates of viral or cellular tyrosine-specific protein kinases, which have not yet been identified by other methods. (Author abstract) (31 Refs)

21. SIMILAR GLYCOPEPTIDES IN NORMAL CHONDROBLASTS AND IN ROUS SARCOMA VIRUS-TRANSFORMED FIBROBLASTS.

Cossu G, Warren L, Boettiger D, Holtzer H, Pacifici M
(c/o Pacifici) Dept. Anatomy G3, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104
J Biol Chem; 257(8):4463-4468 1982

Fucose-labeled glycopeptides were isolated from the glycoproteins of normal chick embryo chondroblasts grown in monolayer cultures or in suspension. Analysis by chromatography on Sephadex G-50 columns revealed that a large proportion of these glycopeptides co-migrated with the large mol wt glycopeptides (Group A) reported in numerous types of tumorigenic cells. the proportion of Group A glycopeptides in normal chondroblasts was essentially identical with that found in chick embryo skin fibroblasts transformed by a temperature-sensitive mutant (ts-LA24A) of Rous sarcoma virus and grown at the permissive temperature. When chondroblasts transformed with ts-LA24A were grown at either the permissive or the nonpermissive temperature, no changes were observed in the overall pattern of glycopeptide synthesis or in the amount of Group A glycopeptides synthesized. Furthermore, when the various glycopeptides synthesized by normal and transformed chondroblasts were compared by concanavalin A-Sepharose affinity chromatography and DEAE-Sephadex ion exchange chromatography, no significant differences were found. The unusually high level of Group A glycopeptides found in monolayer or in suspension cultures of normal chondroblasts appears to be under environmental control. Thus, normal chondroblasts in vivo, as well as in organ culture, did not synthesize the large proportion of Group A glycopeptides, and the overall pattern on Sephadex G-50 column chromatography was indistinguishable from that of normal skin fibroblasts. We conclude that (1) normal chondroblasts in monolayer or suspension cultures can be induced to synthesize a class of molecules characteristic of transformed cells, and (2) though the synthesis of these glycopeptides may not be a prominent part of the normal in vivo biosynthetic program of chondroblasts, their synthesis in vitro probably reflects a response or adaptation to differences in their microenvironment. (Author abstract) (31 Refs)

22. LOSS OF DIFFERENT PERICELLULAR MATRIX COMPONENTS OF RAT CELLS TRANSFORMED WITH A T-CLASS TS MUTANT OF ROUS SARCOMA VIRUS.

Alitalo K, Keski-Oja J, Hedman K, Vaheri A

Dept. Microbiology and Immunology, Sch. Medicine, Univ. California, San Francisco, CA, 94143

Virology; 119(2):347-357 1982

Rat cells transformed by the T-class ts mutant LA339 derived from SSV B77 (2R cells) and the parental nontransformed Rat-1 cells were analyzed for the production and deposition of pericellular matrix components as a function of growth temperature. The cells were incubated at the permissive (35 C) and nonpermissive (39.5 C) temperatures for transformation and the collagenous and noncollagenous (fibronectin and laminin) matrix proteins were studied by polypeptide analysis of the metabolically labeled cells and their culture media. Immunofluorescence analysis of the pericellular matrix staructures was performed using specific antibodies against laminin, fibronectin, and heparan sulfate proteoglycan. At 39.5 C dense pericellular matrices were detected in both 2R and Rat-1 cell layers, whereas at 35 C the 2R cells lost their pericellular matrix structures. The cells continued to synthesize and secrete fibronectin, laminin, and heparan sulfate proteoglycan as well as slightly reduced amounts of procollagen into the culture medium but failed to deposit them in a matrix form. Another major temperature-sensitive difference in the secreted polypeptides was the production by the 2R cells at 35 C of a 56,000-dalton protein, similar to that reported in other transformed cell cultures. The present findings indicate that the transformed rat 2R cells lose, upon activity of the pp60src, their capacity to deposit the synthesized matrix components into pericellular structures. (Author abstract) (48 Refs)

23. TRANSCRIPTION OF GLOBIN GENES IN CELLS TRANSFORMED BY RAUSCHER VIRUS.

Peresleni TIu, Mechetner EB, Rozinova EN, Dvorkin GA

Inst. General Genetics, Moscow, USSR

Biokhimiia; 47(2):312-316 1982

The content of globin messenger RNA (mRNA) was studied in cultured cells of Rauscher erythroleukemia (REL) and in spleen of mice with REL. Molecular hybridization of globin complementary DNA with cytoplasmic RNA showed virtual absence of mRNA in REL cells. These findings indicate that impairment of Hb synthesis in REL is associated with the absence of mRNA and not with the impairment of its translation. (16 Refs) (In RUS)

24. CALMODULIN AND CA2+ IN NORMAL AND TRANSFORMED CELLS.

Veigl ML, Sedwick WD, Vanaman TC
Dept. Microbiology and Immunology, Duke Univ. Medical Center, Durham, NC, 27710
Fed Proc; 41(7):2283-2288 1982

Numerous lines of evidence implicate calcium and calmodulin (CaM) as regulators of cell growth and functional differentiation. In light of this evidence, several studies of the possible involvement of the CaM system in cellular transformation by RNA and DNA tumor viruses have been carried out. This paper summarizes the evidence linking calcium and CaM to the regulation of cell growth and critically examines the evidence that increases in CaM levels occur in transformed versus normal cells. A nontraumatic method for synchronizing both normal and transformed chick fibroblasts is presented. This method is utilized in a comparison of CaM levels throughout the cell cycle of Rous sarcoma virus transformed and normal chick embryo fibroblasts. These studies best support the hypothesis that the observed differences in CaM levels between transformed and normal cultures under optimal growth conditions may largely reflect differences in the proportion of cells in a dividing versus a nondividing state. (Author abstract) (41 Refs)

25. ECOTROPIC MURINE LEUKEMIA VIRUS DNA CONTENT OF NORMAL AND LYMPHOMATOUS TISSUES OF BXH-2 RECOMBINANT INBRED MICE.

Jenkins NA, Copeland NE, Taylor BA, Bedigian HG, Lee BK
Jackson Lab., Bar Harbor, ME, 04609
J Virol; 42(2):379-388 1982

BXH-2 recombinant inbred mice spontaneously produce a B-tropic murine leukemia virus (MuLV) beginning early in life and have a high incidence of non-T-cell lymphomas. These traits are not characteristic of the progenitor strains (C57BL/6J and C3H/HeJ) or of 11 other BXH recombinant inbred strains. Since B-tropic virus expression may be causally related to the high incidence of lymphoma in this strain, we have analyzed the ecotropic MuLV DNA content of both normal and lymphomatous tissues of BXH-2 mice. Southern analysis and hybridization with an ecotropic MuLV DNA-specific probe showed that DNA of normal BXH-2 tissues contained both parental N-tropic MuLV proviruses but lacked endogenous B-tropic MuLV DNA sequences. In addition, none of 116 F1 hybrid mice derived from male BXH-2 mice spontaneously produced ecotropic MuLV early in life. These results suggest that the B-tropic virus is horizontally transmitted in BXH-2 mice. Southern analysis of DNA from tumor tissues of 12 BXH-2 mice showed that amplification of ecotropic-specific DNA sequences had occurred in lymphomatous tissues of 3 mice and suggested that these tumors were monoclonal. The number of newly acquired proviruses, which appeared to be structurally nondefective and integrated at different sites, varied from one to three copies. Since lymphomatous tissues, from only 3 of 12 mice examined carried additional detectable ecotropic proviruses, these results suggest that amplification of ecotropic MuLV DNA sequences is not required for maintenance of transformation in BXH-2 lymphomas. (Author abstract) (36 Refs)

26. TUMOR VIRUSES AND EARLY MOUSE EMBRYOS.

Kelly F, Condamine H
Unite de Toxicologie genetique, Institut Pasteur, 25, rue du Docteur Roux, 75015 Paris, France
Biochim Biophys Acta; 651(2/3):105-141 1982

Experiments of infection of early mouse embryos with DNA and RNA tumor viruses are reviewed and expression of various types of endogenous RNA viruses is addressed. Viruses discussed include simian virus 40, polyoma virus, Moloney murine leukemia virus, and Type A and C endogenous viruses. Studies performed with embryonal carcinoma cells and simian virus 40, polyoma viruses, and murine RNA tumor viruses are reviewed. (247 Refs)

VIRUS REPLICATION AND EXPRESSION

27. TRANSFER OF MOUSE ANTI-XENOTROPIC VIRUS NEUTRALIZING FACTOR TO HUMAN LIPOPROTEINS.

Levy JA, Dimpfl J, Hardman D, Kane JP
Dept. Medicine, Cancer and Cardiovascular Res. Inst., Dept. Medicine, Sch. Medicine, Univ. California, San Francisco, CA, 94143
J Virol; 42(2):365-371 1982

We examined the migratory properties of the mouse serum protein responsible for specific neutralization of the endogenous mouse xenotropic Type C virus and demonstrated that this neutralizing factor can be transferred from mouse lipoproteins to human and to nonreactive mouse lipoproteins. After acceptance of this activity by these lipoproteins, it could be back-transferred to human and to mouse lipoproteins. This result was compatible with equilibrium binding of the responsible proteins by several classes of lipoproteins. The best expression of the transferred activity occurred with human chylomicrons. Small quantities of neutralizing factor which exist in free dispersion in serum were also detected by mixing the p greater than 1.21 g/ml density fraction of mouse serum with human chylomicrons; antiviral activity was subsequently found associated with the human lipoproteins. This result reflects the potentiation of antiviral activity of the protein in a lipoprotein environment. These observations offer a useful approach for the eventual purification and characterization of the neutralizing factor. (Author abstract) (15 Refs)

28. ENDOGENOUS ONCOGENIC TYPE B VIRUSES IN MICE.

Komarova EA, Kriukova IN
All-Union Cancer Res. Center, Moscow, USSR
Eksp Onkol; 4(2):3-12 1982

Incidence, oncogenicity, and modes of transmission of endogenous mammary tumor type B viruses in different mice strains are reviewed. Biological activity of type B virus was shown to depend upon the virus-host system. The titer of the endogenous virus in the milk depended upon the age and the number of lactations of the females. The incidence of mammary gland carcinoma (MGC) after administration of type B virus depended upon the sensitivity of the mice and the level of natural killer cells. Analysis of specific viral DNA sequences in the cell genome showed the presence of 3-5 provirus copies in high-cancer and low-cancer mice. Recent findings indicated that MGC cells of GR mice contain increased number of the copies of viral genome. The genome of type V endogenous viruses consisted of two subunits. Concentration of phospho-

proteins pp20 and p16 in the endogenous viruses was lower than that in the exogenous type B viruses. Expression of the viral genome during spontaneous and induced carcinogenesis depended upon the hormonal status of the host. (77 Refs) (In RUS)

29. EPSTEIN-BARR VIRUS (EBV) GENOME IN HUMAN LYMPHOMA CELLS AMPLIFIES EXPRESSION OF THE PROVIRAL MURINE LEUKEMIA VIRUS (MULV) P30 (MEETING ABSTRACT)

Lasky RD, Troy FA
Department of Biol Chem, University of California School of Medicine, Davis, CA, 95616
Fed Proc; 41(3):1387 1982

EBV-negative lymphoma lines, Ramos and BJAB, can be converted in vitro to EBV-positive sublines thus providing a uniclonal tumor cell population in which the same line can be compared with and without the EBV genome. We have used this system to distinguish between trivial subline difference and differences related to the presence of the EBV genome. The antigenic profiles of plasma membranes were examined using sera from immunized rabbits. Tumor cells proteins were resolved by SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis) and then electrophoretically transferred to nitrocellulose paper. Anti-tumor cell sera was allowed to bind to the antigens. Binding was detected using 125I-labeled antibodies to the IgG of the primary sera, followed by autoradiography. Electro-blotting revealed several distinct differences. A major difference was an increase in a 30K dalton protein (p30) in the Ramos converted sublines. In contrast, no p30 seen in BJAB or its converted lines. When Ramos, but not BJAB, was originally established in culture, it was passaged in athymic nude mice and acquired an MuLV provirus. Present results suggested that the EBV-genome in Ramos converted cells amplified expression of the mouse p30. This conclusion was confirmed using antisera specific for MuLV and p30. How EBV is promoting enhancement of retroviral proteins in these human lymphoma cells and its possible biological significance is not clear. (no Refs)

30. RAPID PURIFICATION OF EXTRACELLULAR AND INTRACELLULAR MOLONEY MURINE LEUKEMIA VIRUS.

Aboud M, Wolfson M, Hassan Y, Huleihel M
Microbiology and Immunology Unit, Ben-Gurion Univ. of Negev, P.O.B. 653, Beer Sheva 84 120, Israel
Arch Virol; 71(3):185-195 1982

The present study demonstrates the advantages of a combination of concentration by polyethylene glycol-6000 and Sepharose Cl-4B chromatography as a rapid procedure for retroviruses purification. This procedure can be completed within 3 hours, providing a high degree of virus purification with minimal damage to its structural and biological properties. Using transmission electron microscopy we observed many intracellular Type-C virions in cytoplasmic vacuoles of 3T3/NIH cells chronically infected with Moloney murine leukemia virus. There intracellular virions could be isolated from postmitochondrial cytoplasmic fractions prepared from the infected cells by a procedure which minimized its contamination by extracellular free or membrane-bound virions. SDS-polyacrylamide gel electrophoresis showed that the intracellular and extracellular virions contained similar protein composition. (Author abstract) (35 Refs)

GENETICS

31. SUPPRESSION OF SPONTANEOUS MAMMARY TUMORIGENESIS DESPITE MTV-1 GENE EXPRESSION IN HYBRID AND BACKCROSS C3H-AVYFB X C3H/SM MICE.

Smith GH, Henry TJ, Vlahakis G, Arthur LO
Lab. Molecular Biology, NCI, Bethesda, MD, 20205
Int J Cancer; 29(5):591-598 1982

Mouse mammary tumor virus (MMTV)-specific RNA and antigen content of normal and neoplastic mouse mammary tissue were measured in strains C3H/Sm and C3H-AvyfB in C3H-AvyfB female x C3H/Sm male F1 hybrids and in (C3H-AvyfB x C3H/Sm) x C3H/Sm male backcross segregants. The molecular data, along with the relative mammary tumor incidences, suggest that the endogenous MMTV provirus expression gene Mtv-1 present in C3H mice is fully expressed in the C3H-AvyfB subline but is silent or more probably absent in the C3H/Sm subline. Cessation of translational expression of endogenous MMTV occurred only in the agouti backcross females, suggesting an association between this phenomenon and the agouti locus of C3H/Sm. Evaluation of the relative MMTV RNA content of nucleic and cytoplasmic fractions from C3H/Sm mammary tissues strongly suggests that transport and/or processing of MMTV RNA is defective in these mice. This defect probably accounts for the absence of detectable MMTV antigens in C3H/Sm and agouti backcross mammary tissues and tumors and may contribute to the observed reduction in mammary tumor incidence. (27 Refs)

32. TUMORIGENICITY OF PARTIAL TRANSFORMATION MUTANTS OF ROUS SARCOMA VIRUS.

Kahn P, Nakamura K, Shin S, Smith RE, Weber MJ
(c/o Weber) Dept. Microbiology, Univ. Illinois, Urbana, IL, 68103
J Virol; 42(2):602-611 1982

Chicken embryo cells infected with partial transformation mutants of Rous sarcoma virus were tested for tumor-forming ability in chickens and in nude mice. Cells transformed by each of these partial transformation mutants display different combinations of transformation parameters. They therefore present a potentially favorable system for analyzing which properties of transformed cells are necessary for tumor formation. We found that the relative tumorigenicity of the virus mutants was generally similar in chickens and in nude mice, except that certain temperature-conditional mutants appeared to be sensitive to the differences in both temperature of the two experimental animals. (The body temperature of nude mice is 4 to 5 C lower than that of chickens). Thus, the nude mouse appears to be a suitable system for testing the tumorigenicity of transformed chicken cells. Because mice are nonpermissive for Rous sarcoma virus infection and replication, it was possible to recover the transformed chicken cells from the tumors in this host and to determine what phenotypic changes they had undergone during tumor development. We also examined the relationship between various cellular properties of the virus-infected chicken cells in vitro and their tumorigenicity in nude mice. The combined results of these two studies indicated that anchorage independence and plasminogen activator production were highly correlated with the tumor-forming ability of these cells, whereas loss of fibronectin did not correlate with tumorigenicity. Furthermore, the inability of the least tumorigenic virus mutant to stimulate the phosphorylation of a 36,000-Mr target of pp60src raises the possibility that the 36,000-Mr protein plays a role in tumor formation. (Author abstract) (31 Refs)

33. HERITABILITIES FOR REGRESSION AND PROGRESSION OF ROUS SARCOMAS IN THE CHICKEN.

Gyles NR, Johnson LW, Brown CJ, Whitfill CE
Dept. Animal Sciences, Univ. Arkansas, Fayetteville, AR, 72701
Poult Sci; 61(5):835-841 1982

The progressive growth of Rous sarcoma virus (RSV) induced tumors in chickens and the influence of hatch, line and sire, are described. Strong evidence is presented that additive genetic variation is important in the resistance to early RSV-induced tumor growth. Both environmental and genetic components of resistance are implicated. (8 Refs)

34. SEPARATION OF HIGH MAMMARY TUMOR INCIDENCE FROM HIGH HEPATOMA INCIDENCE IN BACKCROSS MICE DURING SEGREGATION OF THE VIABLE YELLOW GENE.

Smith GH, Vlahakis G
Lab. Molecular Biology, NCI, Bethesda, MD, 20205
Int J Cancer; 29(5):587-590 1982

Mammary tumorigenesis in strain C3H/AvyfB female mice (approx 90% incidence) is not due to exogenous mouse mammary tumor virus (MMTV) but to genetic factors transmitted by either parent. Prominent among these genetic factors is the viable yellow (Avy) gene which may increase either the virulence of the endogenous MMTV provirus (Mtv-1) by promoting expression of the susceptibility of the mammary tissue to tumorigenesis by endogenous MMTV. Unexpectedly, the F1 hybrid females (AvyA) developed mammary tumors at a relatively low rate although hepatoma incidence remained high. Both yellow (AvyA) and agouti (AA) backcross females showed an even greater reduction in mammary tumor incidence, 7.9% and 3.8% respectively. In contrast, the high rate of spontaneous hepatoma development segregated with the Avy gene since 86-5% of the yellow (AvyA) backcross females development hepatomas by 19 mo of age, while only 25% of the agouti (AA) backcross females had liver tumors at 24.4 mo. The reduction of mammary tumor incidence in (C3H-AvyfB x C3H/Sm)F1 hybrids was unexpected since earlier studies had shown that reciprocal F1 hybrids between strains BALB/c and C3H-AvyfB continued to show a 90% mammary tumor incidence. The present result is consistent with the possibility that strain C3H/Sm possesses a heritable factor(s) which attenuates the ability of endogenous MMTV to malignantly transform mammary epithelium. (15 Refs)

35. GENETICS: ANIMAL TUMORS.

Heston WE
Lab. Biology, NCI, NIH, Bethesda, MD
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Genetics has helped determine that cancer is not a single disease but a group of different diseases. Genetics has helped integrate the approaches to cancer research for each approach has had to take into account genetic elements. Same form of tumor occurs in the most lowly multicellular organism with little normal cell differentiation, which indicates that the basic neoplastic change involves a very primitive physiological process. Tumors have been studied extensively in invertebrates such as the diploblastic coelenterates and insects. There is evidence among the vertebrates that in the evolution of the species certain gene complexes have been sorted out to give rise to specific tumors in certain species. Tumors have been studied in fish, fowl, birds, and mammals, particularly the rat and mouse. Selectivity of the species has been demonstrated through hybridization studies which indicate that cancer is a negative selective factor in the evolution of species. Inbreeding has been used in cancer research to provide high tumor strains of animals. Other topics reviewed are the genetics of spontaneous tumors, of chemically induced tumors, of hormonally induced tumors, and of virally-induced tumors. (90 Refs)

IMMUNOLOGICAL STUDIES

36. IDENTIFICATION OF AN ANTIGEN ASSOCIATED WITH TRANSFORMING GENES OF HUMAN AND MOUSE MAMMARY CARCINOMAS.

Becker D, Lane MA, Cooper GM
(c/o Cooper), Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Proc Natl Acad Sci USA; 79(10,part1):3315-3319 1982

Sera from tumor-bearing mice immunoprecipitated an 86,000-dalton glycoprotein from extracts of NIH cells transformed by human mammary carcinoma DNA. This antigen was not immunoprecipitated from extracts of NIH 3T3 cells, spontaneously transformed NIH cells, NIH cells transformed by normal human DNA, NIH cells transformed by human bladder carcinoma DNA, or NIH cells transformed by Rous sarcoma virus DNA. In addition, sera from mice bearing tumors induced by NIH cells transformed by either normal human DNA or human bladder carcinoma DNA did not immunoprecipitate this antigen from extracts of NIH cells transformed by human mammary carcinoma DNA. However, this antigen was immunoprecipitated by sera from mice bearing tumors induced by NIH cells transformed by mouse mammary carcinoma DNAs and from mice bearing primary mammary carcinomas. These results indicate that this glycoprotein represents an antigen that is specifically associated with expression of the transmissible transforming genes of human and mouse mammary carcinomas. (Author abstract) (15 Refs)

37. PURIFICATION OF CELL LINE-SPECIFIC TRANSPLANTATION ANTIGENS FROM MOUSE ASCITES TUMOR CELLS.

Tanino T, Saito M, Egawa K
Dept. Cell Chemistry, Inst. Medical Science, Univ. Tokyo, Shiroganedai 4-6-1, Minato-ku, Tokyo 108, Japan
Gan; 73(2):299-307 1982

Tumor-specific transplantation antigens unique to each of MM2, MM46 and Ehrlich mouse ascites tumor cells (cell line-specific antigens) were released from the cells into the medium during incubation in 0.12M saline at 37 C for 30 min. The released antigens were purified by identical procedures which consisted of ultracentrifugation, affinity chromatography using Sepharose 4B conjugated with Ricinus communis lectin, and DEAE-cellulose column chromatography. The recovery was about 700 ug (protein) from 100 g (wet wt) cells. The recovered materials induced specific immunity in C3H/He mice against transplantation of the corresponding tumor cells only when they were administered after treatment with the corresponding tumor-regressor C3H/He mouse serum. Single injection into the peritoneal cavity of 10 ug of each of the pretreated materials inhibited transplantation of 5 x 10(3) corresponding tumor cells. Spleen cells from mice immunized by repeated injections of the pretreated antigen neutralized transplantability of the tumor cells. Specific humoral antibody was also detected. The specific antigens obtained from these cells were similar to each other with respect to sedimentation coefficient (16S), electrophoretic characteristics and xenogeneic antigenicity, and were free of beta-2 microglobulin, murine leukemia virus major structural proteins such as gp70 or p30 and murine mammary tumor virus proteins such as gp55 and p28. (Author abstract) (31 Refs)

38. AMPLIFIED EXPRESSION OF MURINE LEUKEMIA VIRUS (MULV)-CODED ANTIGENS ON THYMOCYTES AND LEUKEMIA CELLS OF AKR MICE AFTER INFECTION BY DUALTROPIC (MCF) MULV.

O'Donnell PV, Nowinski RC, Stockert E
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Virology; 119(2):450-464 1982

Recently, we have shown that several isolates of recombinant, dualtropic (MCF) murine leukemia virus (MuLV) can induce amplification of MuLV gag and env gene-coded antigens on thymocytes of young AKR mice and, subsequently, can accelerate leukemia in these same animals. With respect to env gene-coded antigens, it is unclear whether antigen amplification represents expression of env gene products of the input virus on the surface of infected thymocytes or whether infection by MCF viruses induces the expression other endogenous env gene sequences. Infection by antigenically marked viruses has allowed us to decide between these alternatives. We have found that AKR MCF isolates 69L1, 13, and 247 can be distinguished serologically by specific patterns of reactivity with mouse and rat monoclonal antibodies that recognize 10 distinct epitopes (single antigenic determinants) of AKR ecotropic MuLV gp70 and p15(E) proteins. Accordingly, 1-mo-old AKR mice were injected intrathymically with either MCF 69L1, MCF 13, or MCF 247 viruses and thymocytes of virus-injected mice were then assayed for amplification of specific epitopes at 32-36 days postinjection. Quantitative expression of MuLV antigens was determined by flow microfluorometry using a fluorescence-activated cell sorter. The patterns of reactivity with monoclonal antibodies which were originally determined for each virus in vitro were found to breed true on thymocytes infected in vivo. Moreover, the phenotype of virus recovered in vitro from virus accelerated leukemias was identical to that of the injected virus. Thus, the preleukemic change of MuLV antigen amplification appears to represent expression on thymocytes of env gene products encoded by the infecting MCF viral genome which continues to be expressed in the resulting leukemias without apparent changes in the recombinant env gene. (Author abstract) (36 Refs)

39. MAJOR HISTOCOMPATIBILITY COMPLEX (B): EFFECT ON THE RESPONSE OF CHICKENS TO A SECOND CHALLENGE WITH ROUS SARCOMA VIRUS.

Guyre PM, Zsigray RM, Collins WM, Dunlop WR
Dept. Microbiology, Univ. New Hampshire, Durham, NH, 03824
Poult Sci; 61(5):829-834 1982

Immunity to a second Rous sarcoma virus (RSV)-induced tumor in chickens with varying B blood group genotypes was investigated. Most B2/B2 hosts resisted development of tumor after a second RSV challenge, while all B5/B5 hosts developed tumors after both challenges. Tumor growth was not enhanced when tumorous chickens were rechallenged with RSV. When mixtures of RSV plus sera from uninoculated control chickens were inoculated into susceptible hosts, normal tumor induction resulted. Sera from chickens which complete regressed their primary tumors neutralized RSV, however. Regardless of B genotype, levels of serum IgG in F4 crosses at 0, 11, 14, and 21 days postinoculation did not differ significantly. Both humoral and cell-mediated antitumor immunity may be important in resistance to early RSV-induced tumor growth. (15 Refs)

40. MHC-DEPENDENT MODULATION OF THE MATURATION OF ANTI-TUMOR IMMUNITY IN THE CHICKEN (MEETING ABSTRACT)

Watanabe DH, Chalmers JH, Strebel FR, Cutting JA, McBride RA
Department of Pathology, Baylor College of Medicine, Houston, TX, 77030
Fed Proc; 41(3):332 1982

In two related inbred lines of chickens (G-B1 and G-B2), previous work demonstrated that inoculation of 3-4 week old chicks with Schmidt-Ruppin-RSV (Rous Sarcoma virus)-B induces tumors which are fatal in line G-B1 but which are largely rejected by line G-B2. Analysis of segregants demonstrated that the G-B2 resistance is MHC (major histocompatibility complex) (B6 haplotype)-associated and is a dominant trait. We now report the results of inoculating SR-RSV-B into groups of chicks of different ages. Immunity in line G-B2 appears after 1 week (0% survival) and is fully effective following inoculation at 4 weeks (100% survival). G-B1 birds (B13 haplotype) are not resistant even when inoculated at 6 weeks (0% survival). In contrast, during weeks 1-4, (G-B1 x G-B2)F1 progeny are at first more resistant than G-B2 chicks of the same age. Haplotype-associated resistance in progeny of the backcross mating (G-B1 x G-B2)F1 x G-B2 was: B13/B6 equals 21/23(91%) and B6/B6 equals 10/21(48%) when inoculated at 21 days and; B13/B6 equals 18/19(95%) and B6/B6 equals 11/12(92%) for inoculation at 27 days. These results indicate that the B13 haplotype complements the B6 haplotype by hastening the expression of B6-dependent resistance. This MHC-dependent differential maturation of anti-tumor resistance during ontogeny is probably dependent on Ir loci and may reflect asynchrony of Ir gene expression during development. (no Refs)

41. REJECTION OF TUMOR GRAFTS AFTER PASSAGE OF THE TUMOR CELLS IN VITRO: FAILURE TO CORRELATE ATTENUATED GROWTH IN VIVO WITH PRESENCE OR LOSS OF VIRAL PRODUCTS THAT SUPPRESS MACROPHAGE FUNCTIONS (MEETING ABSTRACT)

Johnson RJ, Shin HS
The Johns Hopkins University School of Medicine, Baltimore, MD, 21205
Fed Proc; 41(3):845 1982

The C3H lymphoma 6C3HED, following passage in vitro, can become immunogenic. Although the initial rate of growth after reinoculation in vivo is unaltered, such attenuated tumors are eventually rejected. We investigated whether the loss of either lactic dehydrogenase virus (LDV) or the p15E component of the Friend-Moloney-Rauscher murine leukemia viruses correlated with the attenuated state, since these agents have been implicated in suppression of monocyte macrophage functions. The presence of LDV was ascertained by whether there was a characteristic serum increase in LD levels following tumor injection. The expression of P15E by tumor cells was determined by binding monoclonal anti-p15E antibody to fixed cells. The presence of LDV, the presence of p15E, and the in vivo growth pattern of the parental wild type tumor, and two in vitro cell lines were compared. The parental tumor was LDV positive, p15E positive, and showed unattenuated growth. One in vitro cell line was LDV negative, p15E positive, and showed unattenuated growth. The other was LDV negative, p15E positive, and showed attenuated growth. Therefore, there was no direct relationship between the presence or absence of either viral agent with attenuation. (no Refs)

42. VACCINATION AGAINST BOVINE LEUKEMIA VIRUS (BLV) INFECTION (MEETING ABSTRACT)

Theilen G, Ruppanner R, Miller J
Department of Surgery, University of California, Davis, CA, 95616
Proc Am Assoc Cancer Res; 23:1094 1982

An attempt has been made to protect cattle against BLV infection using viable and lyophilized BL-3 lymphoid cell suspension cultures. One group of 6 month-old cattle were vaccinated once with viable BL-3 cells alone and 2X with 10% suspension of aluminum hydroxide adjuvant pH 7.2. Another group of 6 month-old cattle were vaccinated 3X with lyophilized BL-3 cells with 10% suspension of aluminum hydroxide adjuvant pH 7.2. Control and vaccinated cattle were challenged 2 weeks after the last vaccination with viable BLV using 2.5x10(5) infected lymphocytes. Results indicated a protective factor in the BL-3 cells. To test the long term effects of vaccine, young uninfected cattle were vaccinated in a commercial herd in which there is a high rate of BLV infection in adult cattle. About 6 months post vaccination cattle were challenged by contact exposure and continuously thereafter. Results of the long term nature exposure trial are pending. The protective factor is unknown although it is not BLV or a subunit protein because BL-3 cells are not BLV producers. Protective factor probably is tumor associated transplantation antigens since BL-3 cells are a continuous cell line derived from a calf with lymphoma. Test and slaughter programs have proved successful in elimination of BLV infection in some countries but it would be economically prohibitive in countries with widespread BLV infection rates, such as the USA and Canada. (no Refs)

43. RETROVIRUS IMMUNOTHERAPY OF CANINE LYMPHOMA (MEETING ABSTRACT)

Miller CH, Gardner MB, Couto G, Theilen G
University of California Davis, School of Medicine and Veterinary, Medicine Davis, CA, 95616
Fed Proc; 41(3):335 1982

Canine lymphoma was treated by immunostimulation using endogenous baboon type C retrovirus (BaEV) in combination with chemotherapy. The rational is, following reduction of the tumor burden by chemotherapy, BaEV will preferentially infect residual tumor cells and illicit new surface antigens at the site of virus budding. This approach was instituted following evaluation of mean remission times on animals with generalized lymphoma using chemotherapy: cytoxin, oncovin ARA-C (cytosine arabinoside), prednisone, (COAP) or BaEV immunostimulation alone. Thirty dogs with total clinical remission given only COAP exhibited mean total remission times of 30 days after stopping chemotherapy. Six of fourteen dogs (43%) given BaEV alone demonstrated dramatic partial remission (50% node reduction) that lasted from 2-14 weeks before new masses occurred. Assays confirmed a transient viremia followed by production of specific antiviral antibodies. Mean survival among the 6 responders was 4.6 months whereas the nonresponders survived 1 month. These results prompted a pilot study combining chemotherapy and immunotherapy. Four dogs in clinical remission after chemotherapy were injected with virus. The mean total clinical remission time was 50 days which indicates possible usefulness of virally induced immunostimulation as an adjuvant to chemotherapy in canine lymphoma. (no Refs)

44. USE OF SEPHAROSE BEAD IMMUNOFLUORESCENCE ASSAY FOR COMPARISON OF THE TYPE D RETROVIRUSES MPMV AND PMFV.

Micheel B, Uckert W, Denner J, Fiebach H, Wunderlich V

Dept. Experimental Clinical Immunology, Central Inst. Cancer Res., Acad. Sciences GDR, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany

Arch Geschwulstforsch; 52(4):275-282 1982

Experiments using the Sepharose bead immunofluorescence assay (SBIFA) for comparing Mason-Pfizer monkey virus (MPMV) and a type D retrovirus isolated from a continuous human fibroblast line (PMFV) are reported. MPMV p27 related antigens were demonstrated in experiments using sandwich SBIFA and in those using competition SBIFA. The p15 of PMFV contained antigenic determinants not present in MPMV. Both viruses reacted almost identically in the PMFV p27-specific assay, while there was no reaction of MPMV and a distinct reaction of PMFV in the PMFV p15-specific assay. (19 Refs)

45. GENETIC CONTROL OF THE ANTIBODY RESPONSE TO MURINE LEUKEMIA VIRUSES (MEETING ABSTRACT)

Brown MA, Green WR, Nowinski RC

Fred Hutchinson Cancer Research Center, Seattle, WA, 98104

Fed Proc; 41(3):295 1982

The genetic control of antibody response to proteins of murine leukemia viruses was investigated. Since the antibody response to ecotropic gp70 envelope protein has previously been shown to be linked to the H-2 complex in mice by segregation analysis, more precise mapping was carried out using a panel of B10 congenic mice immunized with AKR ecotropic MuLV. Sera from immunized mice were tested in a radioimmune precipitation assay and the specificity of antibodies demonstrated by polyacrylamide gel electrophoresis. The results confirm that genes within the H-2 complex of mice control the ability to respond to ecotropic gp70. Mice of the H-2b and H-2d haplotypes were responders and mice of the H-2R haplotype were non-responders. The response was dominant in F1 crosses between responder and non-responder parents. Preliminary results employing a series of B10 H-2 recombinant mice have mapped the gene to the I-B region. Control of the antibody response to other viral component proteins such as the p30 core protein was also influenced by H-2 region genes but there was no correlation between the ability to respond to p30 and the ability to respond to gp70. These results were in contrast to the genetic control of response to xenotropic viral proteins. Control of antibody response to xenotropic gp70 was not linked to H-2 and response was recessive in F1 crosses. These findings suggest that different mechanisms may operate in the generation of immune response to ecotropic and xenotropic viral proteins. (no Refs)

46. ACCESSORY CELLS IN THE IN VITRO GENERATION OF TYPE C VIRUS-SPECIFIC T-KILLER LYMPHOCYTES. III. TWO METHODS OF ANTIGEN PRESENTATION TO CYTOLYTIC T-LYMPHOCYTE PRECURSORS.

Wybier-Franqui J, Gomard E, Levy JP
Laboratoire Immunologie et Virologie de Tumeurs, INSERUM U 152, CNRS ERA 781, Hopital Cochin, 75674 Paris Cedex 14, France
Cell Immunol; 68(2):287-301 1982

F1 hybrid mice primed in vivo with tumor cells bearing the virus-induced FMR antigen and the H-2 specificities of each parent are able to produce in vitro in secondary response cytolytic T lymphocytes (CTL) reacting with FMR in the context of the H-2 antigens of both parents. This suggests that the processing in vivo of the immunizing cells by F1 macrophages results in the presentation of FMR antigens in the context of both H-2 specificities. It has also been suggested that FMR antigens are recognized by cytolytic T-lymphocyte precursors (CTL-P) at the surface of tumor cells and not of macrophages. The results reported here show that there are two methods of CTL-P priming: (a) in most cases, FMR antigens are presented directly by the tumor cells; (b) however, in the absence of antigen-presenting tumor cells in vivo or in vitro, macrophages present FMR to CTL-P. The presentation by macrophages appears less efficient but is probably sufficient to explain the priming of memory cells corresponding to both parental H-2. (Author abstract) (17 Refs)

47. LOSS OF THE SHORT LIVED SUPPRESSIVE FUNCTION OF PERIPHERAL LEUKOCYTES IN FELINE RETROVIRUS-INFECTED CATS (MEETING ABSTRACT)

Stiff MI, Olsen RG
Department of Veterinary Pathobiology, Ohio State University, 1925 Coffey Road, Columbus, OH, 43210
Proc Am Assoc Cancer Res; 23:1097 1982

This research examined the short-lived suppressive function of normal and retrovirus-infected (FeLV, feline leukemia virus) cat peripheral blood mononuclear cells (PBMC). Normal specific-pathogen-free cats (SPF) demonstrated an increased lymphocyte blast transformation (LBT) with a suboptimal amount of concanavalin A (con A, 0.1 ug/10(5) PBMC) after a 24 hour delay in mitogen addition as compared to 0 hour mitogenesis. The suppressive removal index (SRI) was calculated by a delta 24 hour mitogenesis /delta 0 hour mitogenesis. Increased stimulation after 24 hours which was not due to enhancing factors accumulating in the culture medium has been attributed to a short-lived suppressor cell function. The average SRI for normal SPF cats was 3.8. This phenomenon was subsequently studied in retrovirus-infected (FeLV) cats who demonstrated a loss of this function with an average SRI of 1.1 which was significantly lower than uninfected animals. This lower index was a result of a higher 0 hour mitogenesis. Therefore, this data suggests a loss of suppressor function during the viremic stages of feline leukemia which may be due to an overall immunosuppression of cellular immune functions including suppressor cells. Ultimately loss of suppressor cells may contribute to the findings of a Coomb's positive anemia associated with feline leukemia pathogenesis. (no Refs)

48. AUGMENTATION OF NATURAL CELL-MEDIATED CYTOTOXICITY BY ADMINISTRATION OF LENTINAN IN MICE.

Sendo F, Seiji K, Fuyama S, Watabe S, Arai S, Herberman RB, Hashimoto Y, Oaki T
Dept. Pathology, Yamagata Univ. Sch. Medicine, Zao, Iida, Yamagata, Japan
Excerpta Med Int Congr Ser; 576:178-187 1981

The effect of Lentinan (L) (2-5 mg/kg im for 3 consecutive days) on natural killer (NK) and natural cytotoxic (NC) activity was investigated in spleen cells of mice. NK activity was measured by 51Cr release, NC activity by 3H-uridine release of the tested in vitro cell lines. L increased NC activity of BALB/c cells against Meth A (methylcholanthrene-induced) fibrosarcoma. With cells from a radiation-induced lymphoma (RLmale1: RIL), L increased NK activity in 4/5 experiments, compared to the control group. This increase was less than the increase of NC activity seen with Meth A cells. In more limited experiments with cells of a Moloney murine leukemia virus induced lymphoma (YAC-1), L increased NK activity. In experiments in (C57BL/6 x BALB/c) F1 mice, there was no significant difference in NC cell activity (compared to controls) on Meth A cells or NK activity on RIL cells. Results suggest that it may be possible to augment natural cell-mediated cytotoxicity through non-interferon pathways, since L does not effect this route, and that this augmentation may vary with the strain of animal. (16 Refs)

OTHER RELATED STUDIES

49. THE EFFECT OF DEXAMETHASONE ON THE INITIATION OF BETA-GLOBIN GENE TRANSCRIPTION IN DIFFERENTIATING FRIEND CELLS.

Mierendorf RC, Mueller GC
(c/o Mueller) McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
J Biol Chem; 257(8):4496-4500 1982

Plasmid subclones of the 5' and 3' regions of the betamajor-globin gene have been used as probes to assay the level and character of the transcripts of this gene in differentiating Friend erythroleukemia cells treated with dexamethasone. Using an S1 nuclease protection protocol, it is shown that dexamethasone reduces the amount of precursor-specific sequences in differentiating Friend cells within 30 min without significantly affecting the nuclear turnover of these molecules. The sites of initiation and termination of transcription remained the same during the shutdown of transcription by the hormone. In contrast to the situation in Friend cells, dexamethasone failed to inhibit globin gene transcription in three normal erythroid tissues. The manner in which the Friend virus complex might render the globin genes sensitive to glucocorticoids is discussed. (Author abstract) (37 Refs)

50. INTERFERON-INDUCED CHANGES IN THE EXPRESSION AND TOPOGRAPHY OF H-2 ANTIGENS AND RECEPTORS FOR SRBC IN TUMOUR CELLS.

Capkova J, Peknicova J, Hajnicka V, Borecky L
Inst. Molecular Genetics, Czechoslovak Acad. Sciences, 142 20 Praha, Czechoslovakia

Folia Biol (Praha); 28(1):28-42 1982

The expression of the H-2 antigens and its changes after interferon (IFN) treatment were studied in methylcholanthrene (MCA) and mouse sarcoma virus(MSV)-transformed clones of C3H mouse embryonic fibroblasts. Topography of H-2 antigenic determinants on the cell membrane and the availability of receptors for sheep red blood cells (SRBCs) were also studied. Both MCA- and MSV-treated cells absorbed anti-H-2.23 (H-2Kk) antibody more effectively than did the control C3H cells; the MCA-treated cells were more effective than the MSV-treated clone. After IFN treatment, one MCV-treated clone showed increased absorbing capacity for H-2DK antibody, and that clone plus another showed increased absorbing capacity for H-2Kk antibody. The effect of IFN on the topography of H-2 determinants as measured by the blocking index was variable, depending upon the MCA-treated clone used and the genetic determinants of H-2 antigenic activity responding to the antisera used. Rosette-forming capacity with SRBCs differed between the two MCA-treated clones; one responded to IFN treatment by greater rosette formation; the other did not. Enhancement of H-2 antigen expression after IFN treatment apparently was the result of change in the spatial relationship of H-2 determinants on the cell surface rather than an actual increase in the number of H-2 antigenic receptors. (37 Refs)

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VIRUS ISOLATION AND CHARACTERIZATION

1. CHARACTERIZATION OF DUALTROPIC TYPE C RETROVIRUSES ISOLATED FROM SPONTANEOUS NON-T LYMPHOMAS OF SJL/J(V+) MICE.

De Rossi A, D'Andrea E, Chieco-Bianchi L
Laboratorio di Oncologia, Istituto di Anatomia Patologica, Via Gabelli 61, 35100 Padova, Italy
Tumori; 68(2):95-104 1982

Endogenous XC- viruses were isolated from non-T spontaneous lymphomas of SJL/J(v+) mice. These isolates were cloned by limiting dilution procedure and characterized for biological and immunological properties. At the electron microscope these isolates showed typical retrovirus Type C morphology. Reverse transcriptase and immunofluorescence assays showed that these viruses were infectious for mouse and heterologous cell lines. Since some of the isolates induced cytopathic foci in mink lung cultures, they had properties similar to those described for other recombinant dualtropic viruses. Using a panel of monoclonal antibodies against gp 70 and p 15 (E) viral proteins, it was observed that the dualtropic XC- viral

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isolates had an antigenic profile different from that of SJL ecotropic XC+ virus. (Author abstract) (37 Refs)

2. POSSIBLE ROLE OF A RETROVIRUS IN THE EXPRESSION OF TUMOR-SPECIFIC ANTIGENS OF THE METH A SARCOMA.

DeLeo AB, Chang KS, Wivel NA, Appella E, Old LJ, Law LW
Sloan-Kettering Cancer Center, New York, NY
Int J Cancer; 29(6):687-693 1982

The serologically defined tumor-specific surface antigen (TSSA) of the chemically-induced BALB/c Meth A sarcoma, highly restricted to 1 of 20 sarcomas of BALB/c origin, has been detected on a Moloney murine sarcoma virus (MoMuSV)-transformed BALB/c3T3 cell line, designated 11A(v). The immunogenicity of the 11A(v) cell in tumor-rejection assays was specific for the Meth A sarcoma, supporting the evidence for a close relationship between the TSSA and the tumor-associated transplantation antigen (TATA) of this tumor. Infection of SC-1 cells with retroviruses present in cultured filtrates of IIA(v) cells resulted in Meth A antigen expression. The retroviruses associated with Meth A antigen expression have been tentatively identified as replication and/or transformation-defective XC-MuLV. The possible roles of MoMuSV and cellular genes of the BALB/c strain of mice in the expression of the Meth A antigen are discussed. (Author abstract) (43 Refs)

VIRUS ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

3. MORPHOLOGICAL, IMMUNOLOGICAL, AND BIOCHEMICAL ANALYSES OF CHICKEN SPLEEN CELLS TRANSFORMED IN VITRO BY RETICULOENDOTHELIOSIS VIRUS STRAIN.

Shibuya T, Chen I, Howatson A, Mak TW
Dept. Medical Biophysics, Ontario Cancer Inst., Univ. Toronto, Toronto, M4X 1K9, Canada
Cancer Res; 42(7):2722-2728 1982

Reticuloendotheliosis virus strain T (REV-T) is a highly oncogenic avian retrovirus which causes a rapid neoplastic disease of the lymphoreticular system. We derived six cell lines from chicken spleen cells infected with REV-T. These cells can produce both the REV-T and its associated reticuloendotheliosis helper virus, REV-A. Histochemical analyses of these cells indicate that, while they are not stained by benzidine, peroxidase, beta-glucuronidase or acid alphanaphthyl acetate esterase, they contain a high proportion (95%) of cells positive for acid phosphatase. Light and electron microscopic studies of these cells also revealed morphologies of lymphoblasts or activated lymphocytes with irregular nuclei and dispersed chromatin. Immunochemical analyses indicate that essentially all (90 to 100%) of the cells contain the surface marker Ia, but no cytoplasmic immunoglobulin M and immunoglobulin G could be detected by immunofluorescence staining. Results also show that some of these cell lines contain a low level of terminal transferase, and a proportion of these cells can be stained by an antiserum directed against chicken bursa cells. These results are consistent with the conclusion that the cells transformed by the highly oncogenic REV-T are lymphoid in nature. In addition, at least some of these cell clones may contain features characteristic of activated B-lymphocytes. Analysis of these cell clones indicates that some cell lines contain an adherent and nonadherent population with some differences in morphologies. In addition, electron microscopic examination revealed that, while the nonadherent cells are actively producing Type C viruses, Type C viruses are either absent or very rare in the adherent cell populations. These results support the conclusion that some of these cell lines are heterogeneous and contain subpopulations of cells with differences in their ability to produce viruses. (38 Refs)

4. TRANSFORMED CELL LINES DERIVED FROM PROGRESSOR SARCOMA VIRUS (MOLONEY) INDUCED TUMORS. I. DIFFERENCES IN PATHOGENICITY BETWEEN C TYPE VIRUSES FROM PRODUCER AND HELPER VIRUS INFECTED NONPRODUCER CELLS. BRIEF REPORT.

Weiland E, Mussgay M

Bundesforschungsanstalt fur Viruskrankheiten der Tiere, P.O. Box 1149, D-7400 Tubingen, W. Germany

Arch Virol; 71(4):343-347 1982

Cell lines derived as producers and nonproducers from progressor Moloney sarcoma virus induced tumors showed differences in the rescuability of the viral sarcoma genome and in biological activities of released virus. Restoration of transformation defective variants is demonstrated. (Author abstract) (10 Refs)

5. GROWTH OF MURINE SARCOMA AND MURINE XENOTROPIC LEUKEMIA VIRUSES IN JAPANESE QUAIL: INDUCTION OF TUMORS AND DEVELOPMENT OF CONTINUOUS TUMOR CELL LINES.

Robey WG, Kuenzel WJ, Vande Woude GF, Fischinger PJ

Lab. Viral Carcinogenesis, NCI, Frederick, MD, 21701

Cancer Res; 42(7):2523-2531 1982

The BALB/c murine endogenous xenotropic leukemia virus pseudotype of m1 Moloney sarcoma virus [m1MSV(B-MuX)] was used to productively transform diploid Japanese quail embryo cells. The majority of newly hatched quail inoculated with m1MSV(B-MuX)-transformed quail embryo fibroblast cells rapidly developed tumors which were predominantly locally invasive fibrosarcomas, but metastases were observed in two birds. In two tumor-bearing quail, lymphosarcomas were observed in conjunction with fibrosarcomas. Quail inoculated with m1MSV(B-MuX) virus or quail embryo fibroblast cells infected with helper leukemia virus did not develop tumors. A cell culture derived from one quail tumor was shown to be oncogenic in newly hatched quail. Viruses produced by m1MSV(B-MuX)-infected quail cells or quail tumors had envelope properties of BALB-derived murine xenotropic leukemia virus as measured by host range, interference, and neutralization. Virus structural antigens, proteins with mol wt of 30,000 and 70,000, were detected in tumors and tumor-derived cell lines by immunofluorescence and gel diffusion. Sera from tumored quail had high titers of type-specific BALB-derived murine xenotropic leukemia virus antibodies as determined by neutralization and immunoprecipitation. Antibodies to the putative m1 Moloney sarcoma virus V-mos gene product were not detected in sera from tumored or regressor quail. (Author abstract) (41 Refs)

6. GRANULOPOIESIS LONGEVITY IN CONTINUOUS BONE MARROW CULTURES AND FACTOR-DEPENDENT CELL LINE GENERATION: SIGNIFICANT VARIATION AMONG 28 INBRED MOUSE STRAINS AND OUTBRED STOCKS.

Sakakeeny MA, Greenberger JS
(c/o Greenberger) Joint Center for Radiation Therapy, Dept. Radiation, Therapy Harvard Medical Sch., 44 Binney St., Boston, MA, 02115
JNCI; 68(2):305-317 1982

Longevity of granulopoiesis in corticosteroid-supplemented continuous bone marrow cultures and generation of permanent WEHI-3 dialyzed conditioned medium (DCM)-dependent hematopoietic progenitor cell lines were evaluated for 28 inbred mouse strains and outbred stocks. Cultures from AKR/J, NZW, C58/J, DBA/2J, and C57BL/KsJ mice generated granulocytes for 45-58 wk and released more than 10(5) murine sarcoma virus (MuSV) rescue units of endogenous retrovirus; nonadherent (NA) cells from 50% or more cultures produced permanent WEHI-3 DCM-dependent cell lines. Cultures from 129/J, BALB/cJ, SJL/J, RF/J, CD-1 Swiss, C57BR/cdJ, C57BL/Ka, CBA/J, RFM/Sn, NZB, C3H/HeJ, NIH Swiss [N:NIH(S)], C57BL/10J, C57L/J, SWR/J, HRS/J, and C57BL/6J mice generated granulocytes for 12-38 wk; some released 10(1) -10(2) MuSV rescue units of retrovirus, and NA cells from less than 50% of cultures from all but SWR/J and C57L/J mice produced WEHI-3 DCM-dependent cell lines. Thus longevity of granulopoiesis in mouse continuous bone marrow cultures varies significantly among strains. (Author abstract) (38 Refs)

7. IN VITRO AND IN VIVO EFFECT OF MYCOPLASMA ARTHRITIDIS AND RAUSCHER LEUKEMIA VIRUS ON MURINE PERITONEAL MACROPHAGES.

Maslova TN, Sanin AV, Khorobrykh VV
Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR
Zh Mikrobiol Epidemiol Immunobiol; (4):61-65 1982

The functional state of the peritoneal macrophages was studied in CBA, BALB/c, and BAF1 mice infected with Mycoplasma arthritidis (MA) and Rauscher leukemia virus (RLV). In vitro incubation with MA inhibited the spreading on the glass of macrophages from BALB/c (RLV-sensitive) and BAF1 (RLV-resistant) mice. Similar changes were observed after mixed infection with MA and RLV. RLV monoinfection caused macrophage activation. (15 Refs) (In RUS)

8. PP60SRC-DEPENDENT INCREASE IN ADENOSINE-STIMULATED CAMP FORMATION.

Howard RF, Glossman H, Friis RR, Sheppard JR
(c/o Sheppard) Dight Inst. Human Genetics, Univ. Minnesota, Minneapolis, MN, 55455
Exp Cell Res; 139(2):436-439 1982

Responsiveness to extracellular signals may participate in the control of cell division. This hypothesis was examined by comparing the adenosine responsiveness of Rous sarcoma virus (RSV)-transformed cells and untransformed cells. The results show that RSV-transformed chicken embryo cells (CEC) are more responsive to adenosine than Rous associated virus (RAV)-infected or normal CEC. Experiments using temperature-sensitive, transformation-defective (ts-td) RSV-CEC grown under permissive and restrictive temperatures exhibit the same differences as RSV- and RAV-infected cells, respectively. Moreover, the ts-td virus-infected cells exhibit an enhanced adenosine responsiveness within 1 hr following a shift from the restrictive to the permissive temperature. These data indicate that increased adenosine responsiveness is an early event in RSV-induced transformation of CEC. (Author abstract) (28 Refs)

9. CYTOSKELETAL TARGETS FOR VIRAL TRANSFORMING PROTEINS WITH TYROSINE PROTEIN KINASE ACTIVITY.

Sefton BM, Hunter T, Nigg EA, Singer SJ, Walter G
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
Cold Spring Harbor Symp Quant Biol; 46(part2):939-951 1981

The phosphoamino acid compositions of several cytoskeletal proteins from both normal and transformed cells were analyzed in order to see if any of the proteins could be substrates for pp60src, which is localized in the cytoplasm of transformed cells. Vinculin, one of the proteins studied, contains increased levels of phosphotyrosine in Rous sarcoma virus-transformed cells and therefore may be a primary substrate for pp60src. (80 Refs)

10. MECHANISM OF TRANSFORMATION BY ROUS SARCOMA VIRUS: EVENTS WITHIN ADHESION PLAQUES.

Rohrschneider L, Rosok M, Shriver K
Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
Cold Spring Harbor Symp Quant Biol; 46(part2):953-965 1981

Using several mutants of Rous sarcoma virus which contain partial lesions in the src gene, various molecular events within adhesion plaques of infected chicken embryo cells were examined in order to determine their contribution to the transformed phenotype. The disposition of pp60v-src, vinculin, fibronectin, and stress fibers and the phosphorylation of vinculin on tyrosine within chicken embryo cells infected with partial-transformation mutants are diagrammed. (32 Refs)

11. CLONAL NATURE OF SPONTANEOUS AKR LEUKEMIA: STUDIES UTILIZING THE X-LINKED ENZYME PHOSPHOGLYCERATE KINASE.

Collins SJ, Fialkow PJ
Medical Service, Veterans Admin. Medical Center, 4435 Beacon Ave. South, Seattle, WA, 98108
Int J Cancer; 29(6):673-676 1982

AKR mice heterozygous at the X-linked phosphoglycerate kinase (PGK) locus were used in experiments to determine the number of cells from which spontaneous thymic leukemias (thymomas) develop. Because only one of the two X-chromosomes is active in XX somatic cells, thymic leukemias that are clonal should display either Type A or Type B PGK, but not both, while those that are multicellular in origin may exhibit both enzymes. Spontaneous thymomas from 19 PGK heterozygous animals expressed exclusively (11 tumors) or predominantly (8 tumors) a single enzyme in contrast to non-malignant tissue from these animals which expressed both enzyme types in approx equal ratios. When primary tumors expressing a single or predominant enzyme type were transplanted, the transplanted tumors invariably displayed the PGK phenotype that predominated in the initial tumor indicating that the minor PGK component was not contributed by malignant cells. These results indicate that spontaneous AKR leukemias are clonal. (Author abstract) (16 Refs)

12. THE INCREASE IN HORMONE-STIMULATED ADENYLATE CYCLASE ACTIVITY FOLLOWING ROUS SARCOMA VIRUS TRANSFORMATION.

Howard RF, Friis RR, Sheppard JR, Glossmann H
Rudolf-Buchheim-Institut fur Pharmakologie, Fachbereich Humanmedizin der Justus-Liebig-Universitat Giessen, D-6300 Giessen, W. Germany
J Cell Physiol; 111(3):295-302 1982

Ability of prostaglandin E1 (PGE1) and isoproterenol (ISP) to elevate the intracellular concentration of cyclic AMP (cAMP) was studied in uninfected cells, cells infected and transformed by Rous sarcoma virus (RSV) and Rous associated virus (RAV). Uninfected chicken embryo cells (CEC), cells infected but not transformed by RAV, and RSV-transformed cells in culture immediately synthesized increased amounts of cAMP upon exposure to 10 uM ISP, 10 uM PGE1, or prostaglandin E2. RSV-transformed cells were consistently more responsive to maximal stimulatory concentrations of ISP than uninfected and RAV-infected cells. RSV-transformation was observed to alter the adenylate cyclase activity measured by CEC membrane preparations. The time courses for the hormone stimulation of intact RSV-transformed and RAV-infected cells suggested that the untransformed cells were rapidly desensitized during continued beta-adrenergic receptor stimulation, while the transformed cell cultures continued to respond to ISP. Results indicated that transformed cells possess a greater number of beta-adrenergic receptors, and are more slowly desensitized by stimulatory concentrations of ISP. Membranes prepared from transformed cells specifically bound greater than 5x the quantity of radiolabeled (-)3H-dihydroalprenolol and 125I-iodocyanopindolol as compared with the untransformed cell membranes suggesting that the major difference in the untransformed and transformed cells is in the concentration of membrane beta-adrenergic receptors and the inability of RSV-transformed cells to self-limit their response to specific external stimuli. (43 Refs)

13. TRIGLYCERIDE AND CHOLESTEROL ESTER METABOLISM OF RAT 1 CELLS AND ROUS SARCOMA VIRUS-TRANSFORMED RAT 1 CELLS.

Engeser H
Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11724
Exp Cell Res; 139(2):396-400 1982

The incorporation of 14C-long-chain fatty acids into the neutral lipids of rat 1 cells and B77 Rous Sarcoma Virus-transformed rat 1 cells was compared. Increased labeling of the cholesterol ester and triglyceride fractions was observed in the transformed cells. In temperature shift experiments, using B77 ts src Rous Sarcoma Virus-transformed rat 1 cells, alterations of cholesterol esterification could first be detected 4-6 hr after shift to the permissive temperature. Changes in triglyceride metabolism could be shown as early as 4-6 hr after activation of the transforming gene function. It is concluded that alterations of neutral lipid metabolism are among the early effects of the transformation process. (Author abstract) (25 Refs)

14. PLASMINOGEN ACTIVATOR RELEASED AS INACTIVE PROENZYME FROM MURINE CELLS TRANSFORMED BY SARCOMA VIRUS.

Skriver L, Nielsen LS, Stephens R, Dano K
Tumorbiologisk Laboratorium, Frederik den V's Vej 11, DK-2100 Kobenhavn O, Denmark
Eur J Biochem; 124(2):409-414 1982

We have previously reported the purification of a plasminogen-activating serine protease with an approx Mr of 48,000 from sarcoma-virus-transformed murine cells. We now report that under serum-free conditions the enzyme is released from the cells in an inactive form. After affinity chromatography with 4-aminobenzamidine-cellulose, ion-exchange chromatography and gel filtration, the proenzyme could be obtained from culture fluid as a pure, homogeneous protein as evaluated by polyacrylamide gel electrophoresis with sodium dodecylsulfate. Proenzyme was quantitatively converted to active enzyme by incubation with catalytic amounts of plasmin. Analysis by polyacrylamide gel electrophoresis with sodium dodecylsulfate under reducing and nonreducing conditions showed that the inactive form consisted of a single polypeptide chain with an Mr of approx 48,000, while the active form consisted of two chains with Mr values of approx 18,000 and 29,000, held together by one or more disulfide bridges. The active-site reagent diisopropylfluorophosphate in radiolabeled form was incorporated into the 29,000-Mr chain of the active enzyme, but not into the inactive form. These findings provide conclusive evidence for the existence of an inactive proenzyme to this plasminogen activator and thus demonstrate an additional step in a cascade-like reaction leading to extracellular proteolysis. Regulatory as well as methodological implications of this finding are discussed. (Author abstract) (30 Refs)

15. SCANNING ELECTRON MICROSCOPY STUDIES OF INTERACTION OF PROTEINS AND POLYAMINO ACIDS WITH ERYTHROBLASTS TRANSFORMED BY FRIEND VIRUS.

Krumins SA, Stotzky G
ERRB, NICHD, Building 10, Room 12N206, Bethesda, MD, 20205
Cell Biol Int Rep; 6(5):443-453 1982

The effects of proteinaceous compounds (ovalbumin, concanavalin A, polysarcosine, gelatin, poly-L-lysine, lysozyme) on cell surface characteristics and adhesive properties of cultured HFL/d-tc erythroblasts transformed by Friend virus were studied by scanning electron microscopy. Both surface topography of individual cells and the ability to aggregate were affected by incubation with the compounds. (23 Refs)

16. DIVERSITY AND PATHOLOGY OF THE LYMPHOCYTE.

Govaerts A
Faculte de Medecine, Universite Libre Bruxelles, Brussels, Belgium
Rev Med Brux; 3(4):235-236 1982

Lymphocytes have multiple and diverse functional properties. B lymphocytes have receptors for Epstein-Barr virus. Acute lymphoblastic leukemia corresponds to clonal development of T, B, or null cells. The viral etiology of certain human cancers has been singularly reinforced by the discovery of a retrovirus C in the cells of T lymphoid leukemias. The associations of the Epstein-Barr virus with Burkitt's syndrome and of hepatitis B virus with hepatic cancer, together with the discovery of human T leukemia virus, may lead to new studies that will permit a greater understanding of cancer immunotherapy. (no Refs) (In FRE)

17. THE FIRST REAL HUMAN TYPE-C RETROVIRUS.

Epstein MA
Dept. Pathology, Univ. Bristol, Bristol BS8 ITD, England
Immunol Today; 3(3):61-62 1982

Recent advances with respect to the human T leukemia virus (HTLV) are reviewed. HTLV may eventually be proven the etiological agent in adult T cell leukemia, thus adding HTLV to the known association of Epstein-Barr virus with Burkitt's lymphoma and nasopharyngeal carcinoma and hepatitis B virus with primary hepatocellular carcinoma. Human oncogenic viruses may be responsible for a very significant proportion of human malignant disease worldwide. (7 Refs)

18. MOLECULAR INTERACTIONS OF HIGH ENERGY FUELS AND JET FUELS WITH ONCOGENIC VIRUSES AND ENDOGENOUS VIRUSES.

Blakeslee JR
Dept. Veterinary Pathobiology, Ohio State Univ., Columbus, OH
Molecular Interactions of High Energy Fuels and Jet Fuels with Oncogenic Viruses and Endogenous Viruses. Available from National Technical Information Service, Springfield, VA, as N82-18855:, 110 pp., 1981.

The objectives of this research are to develop rapid in-vitro assays to evaluate the carcinogenic potential of chemicals used by the US Air Force. Snyder-Theilen feline sarcoma virus (ST FeSV), quantitatively transforms human skin fibroblasts following second order kinetics. These studies were performed in order to determine whether chemicals altered ST FeSV transformation in a predictable manner and to correlate the alteration with the carcinogenic or non-carcinogenic activity of the test chemical. The results, to date, show diverse carcinogens classed as: aromatic amines, polycyclic hydrocarbons. Aminofluorenes, hydrazines, asbestos and mycotoxins inhibited virus transformation when virus infected cells (2 hr post-infection) were exposed to test chemical, while non-carcinogenic chemicals had no significant effect on transformation. Triton X-100, acetone, petroleum and shale oil derived JP5; RJ5 and diesel fuel, marine, demonstrated non-carcinogenic activity while formaline demonstrated carcinogenic activity. Experiments designed to show the specificity of the antagonistic effect of known carcinogens are reported. Disulfuram inhibits biotransformation of 1,2 symmetrical dimethyl hydrazine (SDMH) metabolites, azomethane to azoxymethane (ultimate carcinogen) thereby preventing carcinogenic effect of the proximate carcinogen SDMH. Detailed methodology required to ascertain effect of chemicals on ST FeSV pro-virus integration and synthesis are presented. (Author abstract)

VIRUS REPLICATION AND EXPRESSION

19. THYMIC NURSE CELLS ARE THE FIRST SITE OF VIRUS REPLICATION AFTER INOCULATION OF THE RADIATION LEUKEMIA VIRUS.

Houben-Defresne MP, Varlet A, Goffinet G, Boniver J
(c/o Boniver) Lab. Pathological Anatomy, Inst. Pathology B.23, Univ. Liege, Sart Tilman, B-4000 Liege, Belgium
Leuk Res; 6(2):231-241 1982

The role of thymic nurse cells (TNC) in the development of Radiation Leukemia Virus (RadLV) induced thymic lymphomas was studied in C57BL/Ka mice. The 'starting suspension' contained 8-12% of fluorescein isothiocyanate positive cells; in the last fraction, greater than 50% of the TNC were fluorescent, demonstrating that most of the TNC were derived from the thymus outer cortex. All intra-TNC cells appeared to be Thy-1.2 and Lyt-1 positive. Only 75% of the cells were Lyt-2 positive. No budding particles were observed in the starting cell suspension or in the first 'top' fractions recovered during the TNC isolation procedure; the last 'top' fractions contained only a few free blast cells with budding particles. Some lymphoid blast cells within TNC exhibited membrane budding particles. No such features were observed in TNC isolated from normal C57BL/Ka mice. The frequency of infectious centers in the whole thymocyte population was 1/3 x 10(4); 300x more virus producing cells were observed in the lymphoid cell population released from TNC than in the 'starting cell suspension' or in the phosphate buffered saline suspension. In effect, 1 out of 100 cells recovered from TNC could act as an infectious center whereas only 1 out of 30,000 thymocytes did so. The lymphoid nature of the virus replicating cells detected was demonstrated by the fact that removal of macrophages by nylon wool column filtration did not change the frequency of infectious centers in the cells population recovered from TNC. Results showed that a limited subpopulation of subcapsular immature thymocyte can act as specific targets for productive infection with RadLV. (26 Refs)

20. SHUT-DOWN OF VIRUS SYNTHESIS DURING PROGRESSION OF ERYTHROLEUKEMIA INDUCED BY FRIEND VIRUS IN MICE.

Yoosook C
Dept. Microbiology, Faculty Science, Mahidol Univ., Rama 6 Road, Bangkok 4, Thailand
Int J Cancer; 29(6):659-665 1982

Infection of (C57BL/6 x DBA/2)F1 (BDF1) mice with 2,500 FFU of Friend virus complex (FV) resulted in erythroleukemia followed by recovery, at which time virus could not be detected in the spleens of mice, and with splenomegaly (progressor mice) or without splenomegaly (regressor mice). Progressor and regressor mice developed equally high amounts of FV-neutralizing activity in their sera. Progressor mice contained cells capable of producing virus, despite the lack of viral envelope antigen(s) in their spleens. The tropism of FV recoverable from the spleens of secondary recipients, injected with spleen cells from progressor mice, did not show any change, although the viral genome was present in Fv-1-restrictive host for at least 7 wk. When the number of spleen colony-generating cells was enumerated, by the spleen colony assay, the frequency in normal syngeneic and in allogeneic hosts was approx the same at the early stage of erythroleukemia but was about 1,000 times higher in the syngeneic recipients during leukemia progression. These spleen colony-generating cells were considered to be FV-transformed cells capable of self-renewal and capable of generating infectious centers (IC), respectively. Most of these transformed cells might be non-producer leukemia cells. (Author abstract) (28 Refs)

21. COMPARISON OF THE ENZYME-LINKED IMMUNOSORBENT ASSAY WITH AN EARLY POLYKARYOCYTOSIS INHIBITION ASSAY AND THE AGAR-GEL IMMUNODIFFUSION TEST FOR THE DETECTION OF ANTIBODIES TO BOVINE LEUKEMIA VIRUS.

Graves DC, McQuade M, Weibel K
Dept. Microbiology and Immunology, Univ. Oklahoma Health Sciences Center, PO Box 26901, Oklahoma City, OK, 73190
Am J Vet Res; 43(6):960-966 1982

An indirect enzyme-linked immunosorbent assay (ELISA) was developed, using as test antigen a bovine leukemia virus (BLV) glycoprotein complex (94,000 daltons). The specificity of the ELISA was determined by using specific bovine reference sera. There was a positive reaction using reference sera containing antibodies to BLV, but a negative reaction to reference sera containing antibodies to other ubiquitous bovine agents, ie, bovine viral diarrhea virus (BVDV), foamy-like syncytia virus (BSV), and bovine maedi-like (R-29) virus. The sensitivity of the ELISA for detection of antibodies to BLV was compared with that of the early polykaryocytosis inhibition assay (EPIA), which is based on inhibition of BLV-induced early syncytia formation in cell culture, and with the agar-gel immunodiffusion (AGID) test, using the major glycoprotein (gp51) as antigen. The sera that were tested came from cattle in a high occurrence leukemia herd, cattle in a commercial dairy herd, and from blood samples, obtained from cattle from various parts of Oklahoma, submitted to a diagnostic laboratory for diagnosis of BLV infection. There was 96.2% agreement in the results of all sera tested using the three serotests. The greatest number of positive sera (153) were detected by the EPIA, followed by the ELISA (148) and AGID test (148). There was disagreement in the test results of only 16 sera. Of the 200 sera tested from the commercial dairy herd, 61 (30.5%) were positive by the ELISA, 60 (30%) by the EPIA, and 57 (28.5%) by the AGID test. In the 111 sera from the diagnostic laboratory, 45 (40.5%) were positive by the ELISA, 45 (40.5%) by the EPIA, and 47 (42.3%) by the AGID test. With the 102 sera from the high occurrence leukemia herd, 42 (41.2%) were positive by the ELISA, 48 (47%) by the EPIA, and 44 (43.1%) by the AGID test. The indirect ELISA is another serotest that can be used for the diagnosis of BLV infection in cattle. It is specific, equally as sensitive as the AGID test, rapid to perform requiring inexpensive equipment, and may be the preferred serotest for screening large numbers of animals for BLV infection. (Author abstract) (30 Refs)

GENETICS

22. LEUKEMOGENESIS BY GROSS PASSAGE A MURINE LEUKEMIA VIRUS: EXPRESSION OF VIRUSES WITH RECOMBINANT ENV GENES IN TRANSFORMED CELLS.

Famulari NG, Koehne CF, O'Donnell PV

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Proc Natl Acad Sci USA; 79(12):3872-3876 1982

Gross passage A murine leukemia virus (MuLV) derived from extracts of C3Hf/Bi mouse leukemias has been shown to be a virus complex consisting of ecotropic, xenotropic, and recombinant, dualtropic MuLV components. The three virus components were distinguished biochemically by differences in the mol wt and peptide maps of their primary env gene products synthesized in infected cells in vivo and in vitro. Virus expression was studied in primary leukemias induced in C3Hf/Bi mice by Gross passage A virus extracts and by the individual ecotropic and recombinant MuLV components that were isolated in vitro. Our findings suggest that expression of the recombinant MuLV component of the Gross passage A virus complex is necessary and sufficient for the induction of leukemias in C3Hf/Bi mice. In contrast, induction of leukemias by the ecotropic virus component appears to involve generation of a second virus with characteristics of recombinant, dualtropic MuLV. (Author abstract) (33 Refs)

23. UNIQUE FEATURES OF RETROVIRUS EXPRESSION IN F/ST MICE.

Morse HC, Kozak CA, Yetter RA, Hartley JW
Lab. Microbial Immunity, Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Disease, Bethesda, MD, 20205
J Virol; 43(1):1-7 1982

F/St mice are unique in producing high levels of both ecotropic and xenotropic murine leukemia virus. The high ecotropic virus phenotype is determined by three or more V (virus-inducing) loci. A single locus for inducibility of xenotropic murine leukemia virus was mapped to chromosome 1 close to, but possibly not allelic to, Bxv-1. Although the high ecotropic virus phenotype is phenotypically dominant, the high xenotropic virus phenotype was recessive in all crosses tested. Suppression of xenotropic murine leukemia virus is governed by a single gene which is not linked to the xenotropic V locus. (Author abstract) (18 Refs)

24. USE OF H-2:H-7 CONGENIC MICE TO STUDY H-2-MEDIATED RESISTANCE TO FRIEND LEUKEMIA VIRUS.

Wettstein PJ, Blank KJ
Wistar Inst., Philadelphia, PA, 19104
J Immunol; 129(1):358-361 1982

Congenic and double congenic mice expressing different H-7 alleles with varying H-2 haplotypes on the C57BL/10 (B10) background were tested for their susceptibility to Friend virus (FV) infection. Mice expressing the H-7b allele derived from BALB/c were susceptible to FV infection whereas mice expressing the H-7a allele of B10 were absolutely resistant. Coexpression of H-7b and the H-2a and H-2d haplotypes determined high susceptibility; mice expressing both H-7b and H-2b were relatively resistant compared to H-7b mice expressing H-2b or H-2d. Parallel experiments with BALB/c and BALB.B recipients did not demonstrate differences in susceptibility associated with H-2d and H-2b. Mapping experiments with the H-2h4 and H-2i5 recombinants indicated that the gene determining relative resistance to FV-induced spleen focus formation mapped to the K-end (KbAb) of H-2b. Female recipients expressing H-7b, regardless of their H-2 haplotype, were more susceptible to FV infection than their syngeneic male counterparts. These experiments demonstrate the utility of congenic and double congenic strains that define H-7 and Fv-2 on different H-2 haplotype backgrounds for the analysis of Fv-2:H-7:H-2 interactions in determining susceptibility to FV infection. (Author abstract) (22 Refs)

IMMUNOLOGICAL STUDIES

25. EFFECT OF ENDOGENOUS LEUKOSIS VIRUS GENES ON RESPONSE TO INFECTION WITH AVIAN LEUKOSIS AND RETICULOENDOTHELIOSIS VIRUSES.

Crittenden LB, Fadly AM, Smith EJ
U. S. Dept. Agriculture, Agricultural Res. Service, Regional Poultry Res. Lab., 3606 East Mount Hope Road, East Lansing, MI, 48823
Avian Dis; 26(2):279-294 1982

The effect of the presence or absence of the endogenous viral genes ev2 and ev3 on the immunologic and pathologic response of a retrovirus structurally related to ev genes (avian leukosis virus: RAV-1) and of a retrovirus structurally unrelated to ev genes (reticuloendotheliosis-associated virus: chick syncytial virus (CSV)) was examined in three lines of chickens. Chickens lacking ev gene expression and exposed to RAV-1 as embryos or day-olds were more likely to develop a non-neoplastic syndrome characterized by hepatitis, runting, atrophy of the lymphoid organs, and general immunodepression. Chickens lacking ev gene expression, when exposed to RAV-1 after hatching, mounted a very high neutralizing-antibody response to exogenous avian leukosis virus (ALV). The higher immune response to exogenous ALV apparently cleared the viremia from the chickens more efficiently than the lower response observed in chickens expressing these ev genes. The presence or absence of ev3 had no effect on the frequency of chick syncytial virus isolation and CSV-neutralizing activity. Pathology after CSV inoculation included non-neoplastic lesions often associated with reticuloendotheliosis virus. In their effect on immune response and lesions, ev genes are apparently largely specific for agents structurally related to them. (35 Refs)

26. ANTIBODIES TO ADULT T-CELL LEUKEMIA-VIRUS-ASSOCIATED ANTIGEN (ATLA) IN SERA FROM PATIENTS WITH ATL AND CONTROLS IN JAPAN: A NATION-WIDE SERO-EPIDEMIOLOGIC STUDY.

Hinuma Y, Komoda H, Chosa T, Kondo T, Kohakura M, Takenaka T, Kikuchi M, Ichimaru M, Yunoki K, Sato I, Matsuo R, Takiuchi Y, Uchino H, Hanaoka M
Inst. Virus Res., Kyoto Univ., Kyoto 606, Japan
Int J Cancer; 29(6):631-635 1982

A nation-wide sero-epidemiologic survey of adult T-cell leukemia virus (ATLV), detected as anti-ATLA (ATLV-associated antigen), was made in Japan. Sera from adult donors in 15 different locations were screened for anti-ATLA. High incidences (6 to 37%) of antibody-positive donors were found in seven regions, one in northern Japan, and the others in southwestern regions. These areas are ATLV-endemic areas corresponding to ATL-endemic areas. Examination of sera from healthy donors aged 6 to 80 yr in ATL-endemic areas showed an age-dependent increase of seropositive donors with a maximum of about 30% to 40 yr of age. Anti-ATLA was found in all but two of 142 patients with ATL. Anti-ATLA-positive patients with ATL were mainly found in ATLV-endemic areas and only a few in ATL-nonendemic areas. Six patients with cutaneous T-cell lymphoma in ATLV-nonendemic areas gave a negative reaction for anti-ATLA. The geometric mean titer of anti-ATLA of patients with ATL was higher than that of healthy donors. (Author abstract) (9 Refs)

27. HETEROGENEITY OF THE NATURAL HUMORAL ANTI-TUMOR IMMUNE RESPONSE IN MICE AS SHOWN BY MONOCLONAL ANTIBODIES.

Colnaghi MI, Menard S, Tagliabue E, Torre GD
Div. Experimental Oncology A, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via G. Venezian 1, 20133 Milan, Italy
J Immunol; 128(6):2757-2762 1982

Four anti-tumor cytotoxic antibodies, namely, A6 of the IgG2 class and B3, C2, and D1 of the IgM class, were obtained in monoclonal form from hybridization of mouse myeloma cells with spleen cells of normal untreated mice selected for high natural anti-tumor immune responses. The specificity of the four monoclonals was tested by complement-dependent cytotoxicity assay on the reference EL4 lymphoma at different days of in vivo transplant, on normal adult and fetal tissues, on the SC-1 fibroblastic cell line uninfected or infected with a murine ecotropic Type-C virus, and on a panel of murine lymphomas of different origin. The four antibodies had different specificities: the A6 and B3 recognized virus-related structures, the C2 a structure expressed on fetal cells, and the D1 a normal component of fibroblasts. The different classes and specificities of the four monoclonals, as well as their in vitro-demonstrated synergistic cooperation, give support to the hypothesis that the natural humoral anti-tumor cytotoxic immune response could be the result of the cooperative activity of an array of heterogeneous antibody molecules. (Author abstract) (20 Refs)

28. SERA FROM BREAST CANCER PATIENTS CONTAIN AN IGA ANTIBODY TO A BREAST CYST FLUID COMPONENT.

Witkin SS, Richards JM, Bongiovanni AM, Breed CN, Day NK
Dept. Obstetrics and Gynecology, Cornell Univ. Medical Coll., New York, NY, 10021
Clin Immunol Immunopathol; 23(2):358-365 1982

We have previously demonstrated that aspirated breast cyst fluids from women with benign breast disease contained a particulate component (BCF-PC) that reacted with antiserum to the murine mammary tumor virus (MuMTV). Since women with breast cancer contain antibodies and antigens reactive with MuMTV it was of interest to measure the immune response in breast cancer patients to the BCF-PC. Sera were obtained from breast cancer patients prior to surgery and 5 days postmastectomy, from women with benign breast disease and from healthy women. Analysis for antibody to the BCF-PC was by an enzyme-linked immunosorbent assay. IgA from premastectomy breast cancer patients was significantly more reactive with the BCF-PC than was IgA from women in the other categories (p less than 0.001). In contrast, IgG binding to the BCF-PC did not differ among the various groups. It was further demonstrated that the reactivity of IgA from any particular serum for the BCF-PC remained constant for different BCF-PC isolates. Other fractions of breast cyst fluids were unreactive with IgA from breast cancer patients. Determination of serum IgA levels in these women revealed that the mean IgA level was significantly higher in healthy women than in the other categories (p less than 0.001). Individual IgA levels and levels of IgA antibody to the BCF-PC were found to be not correlated in breast cancer patients. These results indicate that the production of a specific IgA antibody to the BCF-PC increases in sera of patients with breast cancer. Lastly, it was shown that preincubation of patients' sera with disrupted MuMTV, but not intact MuMTV, severely reduced subsequent IgA binding to the BCF-PC. The analysis of sera for IgA antibody to the BCF-PC may be of value for the detection of breast cancer or its recurrence. (Author abstract) (20 Refs)

29. IMMUNOPATHOLOGY OF B-CELL LYMPHOMAS INDUCED IN C57BL/6 MICE BY DUALTROPIC MURINE LEUKEMIA VIRUS (MULV).

Pattengale PK, Taylor CR, Twomey P, Hill S, Jonasson J, Beardsley T, Haas M
Dept. Pathology, Univ. Southern California Sch. Medicine, 2025 Zonal Ave., Los Angeles, CA, 90033
Am J Pathol; 107(3):362-377 1982

Combined clinicopathologic and immunomorphologic evidence is presented that would indicate that a murine leukemia virus (MuLV) with the dualtropic host range is capable of producing a clinically malignant lesion composed of immunoblasts and associated plasma cells in C57BL/6 mice. This process, morphologically diagnosed as an immunoblastic lymphoma of B cells using standard histopathologic criteria, was found to be distinctly polyclonal with regard to immunoglobulin (Ig) isotype when analyzed for both surface and cytoplasmic Ig. Further studies demonstrated that this clinicopathologically malignant, dualtropic MuLV-induced, polyclonal immunoblastic lymphoma of B cells in C57BL/6 mice was normal diploid and unable to be successfully transplanted to nonimmunosuppressed syngeneic recipients. Although all serum heavy and light chain components were found to be progressively elevated as the tumor load increased, the polyclonal increase in serum immunoglobulins was most pronounced for mu heavy and kappa light chains (ie, mu greater than gamma2A greater than alpha greater than gamma 2B greater than gamma1; kappa greater than lambda). The dissociation of clinicopathologic and biologic criteria for malignancy in the presently described dualtropic (RadLV) MuLV-induced B-cell lesion is sharply contrasted with the thymotropic (RadLV), MuLV-induced T-cell lymphoblastic lymphoma in C57BL/6 mice. This process is also a clinicopathologically malignant lesion but, when one uses biologic criteria, is found to be distinctly monoclonal, aneuploid, and easily transplanted to nonimmunosuppressed syngeneic recipients. The close clinicopathologic and biologic similarities of the dualtropic MuLV-induced animal model to corresponding human B-cell lymphoproliferative diseases are stressed. (Author abstract) (46 Refs)

30. ISOLATION AND CHARACTERIZATION OF CIRCULATING FELINE LEUKEMIA VIRUS-IMMUNE COMPLEXES FROM PLASMA OF PERSISTENTLY INFECTED PET CATS REMOVED BY EX VIVO IMMUNOSORPTION.

Snyder HW, Jones FR, Day NK, Hardy WD
Lab. Viral Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
J Immunol; 128(6):2726-2730 1982

IgG and circulating IgG immune complexes (CIC) were purified from plasma of three pet cats persistently infected with feline leukemia virus (FeLV) by adsorption to, and elution from, Staphylococcus aureus Cowan I. CIC were then separated from free IgG by sucrose gradient ultracentrifugation and were analyzed for the presence of FeLV structural proteins and corresponding specific antibodies. Radioimmunoprecipitation analysis indicated that FeLV envelope (gp70) and major core (p30) proteins, along with cat IgG heavy and light chains, were present in the CIC from all three cats. Further analysis of the CIC from one of the cats also revealed the presence of FeLV core proteins p15 and p12. IgG purified from isolated CIC was also shown to bind specifically to purified FeLV gp70, p30, and p15. These data provide direct evidence for FeLV-specific CIC in the plasma of persistently viremic pet cats, and suggest these animals are immunologically responsive to the virus even though free antibodies against the major structural proteins cannot be demonstrated in standard assays. (Author abstract) (32 Refs)

31. NATURAL KILLER ACTIVITY AGAINST RETROVIRUS INFECTED CELLS: DICHOTOMY IN NK SENSITIVITY OF INFECTED T AND B CELLS.

Dubey DP, Staunton D, Azocar J, Stux S, Essex M, Yunis EJ
Sidney Farber Cancer Inst., Harvard Medical Sch., Sch. Public Health, Boston, MA, 02115
Clin Immunol Immunopathol; 23(2):215-223 1982

Analysis of the natural killer cell activity against persistently FeLV-infected human T- and B-cell lines HSB-2, RPMI-8402, Raji, and RPMI-8392, and their uninfected counterparts, suggests that feline leukemia virus(FeLV) infection modifies NK sensitivity of T and B cells in different ways. In contrast to infected B cells, which demonstrated a dramatic increase in susceptibility to NK-mediated lysis relative to uninfected cells, infected T (HSB-2 and 8402) cells demonstrated a significant decrease. This pattern of lysis was independent of the NK assay duration. The resistance of NK-mediated cytotoxicity is not due to serum, nor to variation in virus replication in the host cells. This dichotomous response to retrovirus infection suggests different mechanisms of viral interaction leading to the development of specific malignancies through an immune surveillance escape mechanism. (Author abstract) (29 Refs)

32. SENSITIVITY TO MACROPHAGE-MEDIATED CYTOSTASIS IS CELL CYCLE DEPENDENT.

Hamilton TA, Fishman M, Crawford G, Look AT
Div. Immunology, St. Jude Children's Res. Hosp., Memphis, TN, 38101
Cell Immunol; 69(2):363-373 1982

We have examined the sensitivity of proliferating lymphoid cells in different phases of the cell cycle to macrophage-mediated cytostatic activity. These studies evaluated the ability of target cells enriched in individual cell cycle phases to pass into the next phase during brief (2-6 hr) periods of coculture with activated or nonactivated peritoneal macrophages. Both normal (concanavalin A-stimulated spleen cells) and neoplastic (Gross virus-induced thymic lymphoma) cells were analyzed. Spleen cells or lymphoma cells were first separated by centrifugal elutriation into populations highly enriched for G1, S, or G2/M phases of the cell cycle and cultured in the presence of nonactivated or activated macrophages for periods of 2, 4, or 6 hr. The cellular DNA content of recovered nonadherent target cells was then analyzed by flow cytometry after staining with propidium iodide. Macrophage contamination of target cell populations was insignificant under these conditions. Nonactivated macrophages did not affect target cell cycle traverse when compared with target cells cultured alone. Activated macrophage mediated cytostatic activity resulted in complete block of the transition of cells in G1 phase into S phase and of the further accumulation of DNA by cells in early S phase. Cells already in mid to late S phase were able to continue DNA replication at rates nearly equivalent to control cells. There was no inhibition of the passage of cells through G2 or mitosis. These effects were seen as early as 2 hr of macrophage-target cell coculture and both normal and neoplastic cells exhibited identical patterns of cell cycle phase sensitivity. (Author abstract) (21 Refs)

33. CELL-MEDIATED AND HUMORAL IMMUNE RESPONSES OF RATS DURING THE PROGRESSION OF PRIMARY AVIAN SARCOMA VIRUS-INDUCED INTRACEREBRAL GLIOMAS (MEETING ABSTRACT)

Woosley RE, Watkins PJ, Mahaley MS
No affiliation given
1982 Annual Meeting of the American Association of Neurological Surgeons, April 25-29, 1982, Honolulu, Hawaii. American Association of Neurological Surgeons 234 pp., 1982.

The avian sarcoma virus-induced glioma tumor model in the Fischer 344 rat has shown many parallels to the human glioma response. A longitudinal study of the specific immune responses of this tumor model has been studied using an in vitro microcytotoxicity assay monitoring cellular, humoral and antibody-dependent cytotoxicity. These studies were carried out to identify if and when an immune response might occur as the animal developed his tumor so that these responses might be manipulated in future therapeutic protocols. Tumor-bearing animals and their age-matched controls were sacrificed and studied every two weeks, from three to twenty-five weeks after they had been injected intracereberally with avian sarcoma virus at age day five. Other animals were immunized with target tumor cells to serve as an internal cytotoxicity control. Specific cellular (average 12%), humoral (average 5%) and antibody-dependent (average 11%) cytotoxicity of the tumor-bearing animals was not significantly different from their age-matched controls averaging 15%, 5%, and 13%, respectively. Immunized animals showed a significant specific cellular and humoral response averaging 30% and 39% respectively. (no Refs)

34. MURINE T LYMPHOCYTE CLONES: DERIVATION, CHARACTERIZATION AND APPLICATION OF THE STUDY OF ALLOGRAFT AND TUMOR IMMUNITY (MEETING ABSTRACT)

MacDonald HR, Engers HD, Lees RK, Glasebrook AL, Kelso A, Sordat B, Cerottini JC, Brunner KT
Ludwig Institute for Cancer Research, Epalinges, Switzerland
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

Clones of murine T lymphocytes specific for a variety of soluble and cell-bound antigens can now be established and grown in the presence of T cell growth factor (TCGF). We have used this cloning technology to study the immune response to alloantigens and to murine leukemia virus (MoLV)-associated antigens. T lymphocyte clones in both antigenic systems were found to exhibit a variety of functional phenotypes as defined by cytolytic activity and the production of lymphokines such as TCGF, interferon, macrophage-activating factor (MAF), and granulocyte/macrophage colony stimulating factor (CSF). Two approaches were used to investigate the possible role of T lymphocyte clones in allograft and tumor immunity in vivo. In one experimental model, cloned cytolytic T lymphocytes (CTL) were injected intraperitoneally together with dissociated suspensions of 131IUdR (iododeoxyuridine)-labelled tumor target cells bearing relevant alloantigens or MoLV-associated antigens. In both cases, efficient tumor cell destruction was observed; however, when cloned CTL were injected intravenously, only certain clones were capable of recirculating and destroying tumor cells in the peritoneal cavity. In a second model better simulating the complexity associated with solid tumors in vivo, multicellular spheroids of mammary tumor cells were implanted intraperitoneally and exposed to cloned CTL. Again a destruction of tumor spheroids by some (but not all) CTL clones was noted. (no Refs)

OTHER RELATED STUDIES

35. PATHOLOGY OF AN EXPERIMENTAL EXTRADURAL SPINAL T CELL TUMOR.

Kase CS, Wilborn WH, Varakis JN, Cheshire LB, Peterson RD
Dept. Neurology, Univ. South Alabama, 2451 Fillingim St., Mobile, AL, 36617
Lab Invest; 46(5):535-542 1982

Syngeneic mice injected intravenously with a T cell tumor line (line 13) induced by Gross' murine leukemia virus developed paraparesis and sensory loss below the midthoracic level 2 to 3 weeks after inoculation. Although signs of systemic disease coexisted, the animals survived through the development of the neurologic symptoms, and treatment with cytotoxic agents was not required. Pathologic study of the spinal cord and brain revealed tumoral infiltration of the meninges, confined to the extradural spaces, more markedly at spinal than cerebral levels. Equally severe infiltrates occurred in the paravertebral musculature. No leptomeningeal or parenchymal involvement was present, irrespective of the severity of the extradural infiltration. Marked bone marrow and visceral infiltration coexisted with central nervous system involvement. The topography of the extradural and muscular tumor cell collections related to the proximity of the involved bone marrow and areas of direct communication between these spaces were repeatedly identified. On the other hand, line 13 cells injected directly into the brain substance produced diffuse leptomeningeal tumoral infiltration without extradural involvement. These findings suggest that the pathogenesis of this model of spinal T cell tumor proliferation involves a first stage of bone marrow infiltration, followed by extradural involvement. This occurs by direct migration of bone marrow tumor cells through gaps in the vertebral bone. This model offers the opportunity for the study of malignancies that produce bone destruction as a mechanism for tumoral spread. (Author abstract) (29 Refs)

36. LOCAL HYPERTHERMIA THERAPY OF MALIGNANT BRAIN TUMOR USING RADIOFREQUENCY - EFFECTS ON SUBCUTANEOUSLY TRANSPLANTED EXPERIMENTAL BRAIN TUMOR.

Kim T, Tanaka R, Suzuki Y, Sekiguchi K, Yamada N, Saito Y
Dept. Neurosurgery, Brain Res. Inst., Niigata Univ., 1-757 Asahichodori, Niigata 951, Japan
Neurol Med Chir (Tokyo); 22(2):103-110 1982

Anti-tumor effects of radiofrequency hyperthermia on experimental malignant glioma of rats were examined. Radiofrequency electromagnetic fields at 13.56 MHz were used to heat locally subcutaneously-transplanted Rous sarcoma virus-induced rat gliomas. Temperature profiles during radiofrequency treatment showed that the temperature in the tumor was constantly higher by 2 to approx 5 C than that in the surrounding subcutaneous tissue. The tumor temperature was maintained at a stable level throughout the treatment by adjusting the radiofrequency power. Following results were obtained: (1) The critical temperature to bring anti-tumor effects such as delay of tumor growth or extension of the survival of the animals was 43 C. (2) Longer or repeated heating enhanced the anti-tumor effects. (3) Combined therapy consisting of radiofrequency hyperthermia and 60Co-irradiation or an anticancer drug, ACNU (1-(4-amino-2-methyl-5-pyrimidinyl) methyl-3-(2-chloroethyl)-3 nitrosourea), showed greater anti-tumor effects than hyperthermia only. (Author abstract) (37 Refs) (In JPN)

37. RETENTION OF 'METASTATIC' COLONISATION POTENTIAL BY CELLS OF SPONTANEOUS PRIMARY TUMOURS AFTER CRYOPRESERVATION.

Price JE, Tarin D
(c/o Tarin) Dept. Histopathology, Univ. Oxford, John Radcliffe Hosp., Oxford OX3 9DU, England
Br J Cancer; 45(5):790-793 1982

Primary mammary tumors arising in CBA and C3H/Avy mice infected with murine mammary tumor virus were examined. Tumor cells retained their original high or low colonization potential after preservation in liquid N2 for prolonged periods. Technical difficulties are discussed. Applications of the preservation technic are considered. (4 Refs)

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VIRUS ISOLATION AND CHARACTERIZATION

1. IDENTIFICATION OF THE RPMI 8226 RETROVIRUS AND ITS DISSEMINATION AS A SIGNIFICANT CONTAMINANT OF SOME WIDELY USED HUMAN AND MARMOSET CELL LINES.

Popovic M, Kalyanaraman VS, Reitz MS, Sarngadharan MG
Lab. Tumor Cell Biology, NCI, Bethesda, MD, 20205
Int J Cancer; 30(1):93-99 1982

A retrovirus designated RPMI 8226V has been characterized by competition radioimmunoassay (RIA) for the major viral structural protein and by nucleic acid hybridization analysis using cDNA of the virus. In the homologous RIA using rabbit anti-RPMI 8226V and 125I-labeled p36 of RPMI 8226V, RPMI 8226V and SMRV exhibited competition of 81% and 73% respectively. Similarly, in the homologous system for SMRV p36, these viruses competed 98 and 100%. Reagents made from the Type D retrovirus, Mason Pfizer Monkey Virus (MPMV), known to be related but distinct from SMRV, were used in assays designed to detect interspecies determinants of Type D retroviruses. Hybridization analysis of RPMI 8226V

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cDNA showed significant homology to cellular RNA and DNA of mink, bat, and human cells infected with RPMI 8226V and to DNA of SMRV infected cells but not to uninfected cells or cells infected with other viruses. These results taken together clearly indicate that RPMI 8226V and SMRV are very closely related to each other. The finding of a Type D retrovirus in this human myeloma cell line that had been used in EBV studies prompted a survey of RPMI 8226V in some human and marmoset cell lines. The assays included the RIA for p36, nucleic acid hybridization using cDNA of RPMI 8226V, reverse transcriptase analysis, and electron microscopy (EM). The results clearly show that in addition to RPMI 8226, human Burkitt lymphoma cells BJAB/B-95-8/K which were supertransformed by EBV from B-95-8/K marmoset cells as well as marmoset cell lines were positive for the RPMI 8226V. Similar lines obtained elsewhere were negative. The results obtained clearly indicate that RPMI 8226V is a serious laboratory contamination in some widely used human cell lines. The possible impact of this viral contamination for some virological and cell biological studies is discussed. (32 Refs)

2. INDUCTION OF A TRANSFORMING AGENT(S) BY ABORTIVE INFECTION OF HERPES SIMPLEX VIRUS IN THE CELLS CARRYING ENDOGENOUS SARCOMA VIRUS.

Shimizu Y, Kumagai K
Dept. Microbiology, Tohoku Univ. Sch. Dentistry, Sendai, Japan
Excerpta Med Int Congr Ser; 571:29-33 1982

Abortive infection of herpes simplex virus Type 2 (HSV-2) in the murine and hamster cell lines carrying endogenous sarcoma virus induces an agent(s) with in vitro transforming activity in the culture fluids. Two transformed lines positive for murine sarcoma virus but negative for murine leukemia virus were used: D-56 cells derived from murine cell line NIH 3T3, and HT-1 cells derived from a hamster tumor. Normal NIH 3T3 and baby hamster kidney cells and the transformed cells were infected with HSV-2. No increase of virus progeny was seen with either D-56 or HT-1 cells. After cultivation at 37 C for 1 day, the culture fluids were examined for transforming activity using 3T3 or mouse embryo cells which had been treated with diethylaminoethanol-dextran. The exposed cells were subcultured and tested for the appearance of transformed foci in soft agar medium. After 3-4 wk, 2-3 transformed foci/dish appeared only in the 3T3 cell cultures treated with the culture fluids of infected D-56 cells. No foci could be seen with either infected or uninfected 3T3 cells. These results indicate the HSV-2 was not able to replicate in D-56 cells, but did induce an agent(s) with transforming activity in the culture fluids. The possible nature of the agent(s) is discussed. (9 Refs)

VIRUS ASSOCIATED CELL TRANSFORMATION AND HOST ALTERATION

3. HYPERPLASTIC AND NEOPLASTIC ERYTHROPROLIFERATIVE DISEASES INDUCED BY ONCOGENIC MURINE RETROVIRUSES.

Scolnick EM
Lab. Tumor Virus Genetics, NCI, Bethesda, MD, 20205
Biochim Biophys Acta; 651(4):273-283 1982

Structure of Harvey (HV) and Kirsten virus (KV), transforming protein of HV and KV, and Friend virus complex are discussed. Comparison of polycythemia- and anemia-inducing strains of spleen focus-forming virus (SFFV) is presented. Friend murine leukemia virus-induced (F-MuLV) disease and pathophysiology of F-MuLV-induced disease are described. Possible pathophysiological relationships between Friend virus-induced erythoproliferation and Harvey sarcoma virus (Ha-SV)-induced erythroleukemia are discussed. Biochemistry of transforming proteins of erythroleukemia viruses is reviewed. One possible advantage that studies of erythroleukemia have is that the abnormal proliferation of erythroid precursor cells induced by SFFV or Ha-SV is accompanied by a decreased requirement by these cells for erythropoietin. Studies on erythroid cells are limited by the availability of large quantities of purified erythropoietin. Both polycythemia-inducing SFFV and Ha-SV induce the abnormal proliferation of fully hemoglobinized erythroid colonies in cell culture colony assays for the viruses. Results might suggest that Ha-SV infection of stem cells could be a method for generating stem cell lines. (81 Refs)

4. THE PATHOGENESIS OF ABELSON VIRUS LYMPHOMAS OF THE MOUSE.

Risser R
McArdle Lab. for Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Biochim Biophys Acta; 651(4):213-244 1982

The origin of the Abelson virus (AV) and the pathogenesis of the disease it induces are discussed. Before discussing Abelson murine leukemia virus (A-MuLV) in detail, some insights gained from the study of other RNA tumor viruses, both with respect to mechanisms of their action and host genetic responses to them, are presented. The main presentation comprises four sections. Virological and molecular characterization of AV involves its isolation, assays, genome structure of the helper and defective viruses, proteins encoded by the defective A-MuLV genome, and mutants of AV. Biology of AV diseases is discussed in relation to transformation of bone marrow cells by A-MuLV and pathogenesis. Differentiative phenotype of Abelson lymphomas and cell lines is discussed in relation to phenotypes of in vitro-derived lines, expression of lineage markers by tumors, and neoplastic differentiation of clonal Abelson lymphoma lines. With relation to cellular antigens identified on Abelson lymphoma and transformed cells, Abelson target-associated antigen, p50 and Abelson lymphoma antigens are discussed. A final section presents a summary of present knowledge, interpretations and further speculations on the involvement of AV in hematopoietic differentiation and neoplasia. (187 Refs)

5. MODULATION OF ERYTHROPOIESIS BY THE HELPER-INDEPENDENT FRIEND LEUKEMIA VIRUS F-MULV.

Niho Y, Shibuya T, Mak TW
(c/o Mak), Ontario Cancer Inst., 500 Sherbourne St., Toronto, Ontario M4X 1K9, Canada
J Exp Med; 156(1):146-158 1982

Modulation of erythropoiesis in newborn and adult BALB/c mice and adult DBA/2 mice by a replication-independent leukemia virus (F-MuLV) in Friend erythroleukemia virus (FLV) was investigated. Colony-forming unit-erythroid (CFU-E) and burst-forming unit-erythroid (BFU-E) progenitor colony assays were performed following virus infection. A dramatic increase in BFU-E-like colonies was observed in 1-day-old BALB/c mice infected with 3 x 10(5) XC plaque units of F-MuLV, while CFU-E did not increase. BFU-E-like colonies reached a level of approx 1,500 bursts/10(5) cells or approx 5 x 10(7) BFU-E/spleen. Erythropoietic changes were induced in adult

DBA/2 or BALB/c mice when phenylhydrazine (PHZ) was administered in conjunction with F-MuLV. Injection of F-MuLV into PHZ-treated adult mice induced splenomegaly, a decrease in hematocrits, and enhancement of levels of CFU-E. Thus, F-MuLV, without spleen focus-forming virus, can modulate erythropoiesis in newborn and adult mice. Induction of a dramatic increase in BFU-E without an increase in CFU-E implies that the leukemic block in F-MuLV-infected newborn mice is at a stage between BFU-E and CFU-E. These results suggest that F-MuLV may infect different erythroid target cells than the FLV complexes. (39 Refs)

6. PHENOTYPIC DIFFERENCES BETWEEN TUMOR CELLS DERIVED FROM DIFFERENT STAGES OF NEOPLASTIC GROWTH.

Wainberg MA, Germinario RJ
Lady Davis Inst Medical Res., Sir Mortimer B. Davis-Jewish General Hosp., Montreal, Quebec, Canada
Eur J Cancer Clin Oncol; 18(6):545-551 1982

Under conditions employed in our laboratory, tumors which are induced by avian sarcoma virus (ASV) usually grow progressively for several weeks and then regress. In order to further understand the basis for tumor regression in this model, we compared avian sarcoma cells which were cultured from tumors at different stages of development in terms of various phenotypic properties. The results indicate that tumor cells which are derived from progressively-growing sarcomas are rapidly growing, produce large quantities of the enzyme plasminogen activator, and have much in common generally with chicken embryo fibroblast (CEF) cells that have been transformed by ASV. In contrast, tumor cells that are obtained from regressors have elevated levels of hexose transport, grow very slowly, are greatly enlarged and display properties that are characteristic of senescent cells in culture. (Author abstract) (19 Refs)

7. MORPHOLOGICAL EVIDENCE FOR CYCLIC AMP-INDUCED REVERSE TRANSFORMATION IN VOLE CELLS INFECTED WITH AVIAN SARCOMA VIRUS.

Meek WD
Univ. Colorado Health Science Center, Denver, CO, 80262
Mol Cell Biol; 2(7):863-874 1982

Ultrastructural changes that result from dibutyryl cyclic AMP treatment were studied in vole cells. Scanning electron microscopy of the avian sarcoma virus-transformed cells showed the spherical cells covered with microvilli. Filopodia like those seen on mitotic normal cells radiated from the cell body. With fluorescent phalloidin, a rim of actin was noted below the cell membrane of the spherical cells. With an increasing concentration of reverse transformation (RT) agent, more cells became flattended and resembled the normal fibroblasts. Coating the substrate with polylysine did not affect the transformed cell shape when grown in normal medium, but the coated substrate increased the RT response. The ruffling that was common to normal cells occurred in some RT cells, but most cells had rigid, smooth borders. Transmission electron microscopy confirmed the results seen with antitubulin indirect immunofluorescence and the present results with fluorescent phalloidin and antiactin: long tubules ran parallel to the subplasmalemmal microfilament bundles, and intermediate filaments were parallel to the other microfibrils and prevalent in slender processes. Fibronectin was absent on the surface of the transformed vole cell. The long strands which extende from cell to cell in normal cultures were also absent. However, in the RT vole cell, short fibronectin fibrils appeared along the cell periphery. (47 Refs)

8. EFFECT OF REDUCTION OF CULTURE MEDIUM SODIUM, USING DIFFERENT SODIUM CHLORIDE SUBSTITUTES, ON THE PROLIFERATION OF NORMAL AND ROUS SARCOMA VIRUS-INFECTED CHICKEN FIBROBLASTS.

Balk SD, Polimeni PI
Lab. Pathology, New England Deaconess Hosp., Boston, MA
J Cell Physiol; 112(2):251-256 1982

The effects of reduced concentrations of sodium in culture medium on the proliferative behavior of normal and Rous sarcoma virus (RSV)-infected chicken pectoral muscle fibroblasts were studied by substituting choline chloride, tetramethylammonium chloride (TMAC), sucrose, and glucose for part of the sodium chloride. In all cases, the complete test medium contained 42 milliM sodium. Replacement of NaCl with choline chloride resulted in proliferative inactivity in normal fibroblasts and active proliferation in RSV-infected fibroblasts in the presence of 90 milliM Na. Replacement of NaCl with TMAC resulted in both normal and RSV-infected fibroblasts approaching inactivity in the presence of 110 milliM Na and death in the presence of 90 milliM Na. With sucrose, both normal and RSV-infected fibroblasts proliferated at similar reduced rates in the presence of 42 milliM Na, while both normal and RSV-infected cells died quickly in the presence of choline chloride or TMAC substitution. Despite the development of pronounced cytoplasmic vacuolization, both normal and RSV-infected cells in 42 milliM Na medium with sucrose instead of NaCl exhibited reduced but significant proliferation. Unlike sucrose, D-glucose did not cause cell vacuolization. Thus, the effects of reduction of culture medium sodium on cell proliferation differ markedly with the use of different NaCl substitutes. Caution is recommended in drawing inferences about the role of sodium in appropriate and autonomous initiation of cell replication from experimental studies in which the external sodium is reduced. (17 Refs)

9. MAMMARY TUMOR INDUCTION IN INBRED MOUSE STRAINS WITH URETHANE IS NOT ACCOMPANIED BY CHANGES IN EXPRESSION OF B- AND C-TYPE RETROVIRAL STRUCTURAL PROTEINS.

Imai S, Morimoto J, Tsubura Y, Hilgers J
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Int J Cancer; 30(1):101-106 1982

Urethane administered in the drinking water of breeding female mice of five inbred strains (DDf, KF, C3Hf, ddY and C57BL) leads to a higher incidence of mammary tumors at an extremely early age in four of these strains (DDf, KF, C3Hf and ddY). In the case of the DDf strain the tumors are adenoacanthomas, but in the case of the other strains adenocarcinomas are also observed. The effect of urethane in the drinking water on expression of endogenous retroviral structural proteins of the B and C type (MTV and MuLV) was studied in the milk by an immunodiffusion test and in organ extracts by radioimmunoassays (for MTVp27, MTVgp52 and MuLVp30). Organs tested include salivary glands, thymus and spleen from female and male animals. In addition, prostate and seminal vesicles were tested in male animals and uterus and mammary glands in females. Mammary tumors induced by urethane were also tested. Urethane does not induce or enhance endogenous retroviral antigen expression, either in these organs or in the mammary gland, one of the target organs for tumorigenesis by this agent. (Author abstract) (34 Refs)

10. RELATIONSHIPS BETWEEN MORPHOLOGY AND VIRAL ETIOLOGY IN MAMMARY TUMORS OF BALB/CFC3H AND BALB/CFRIII MICE.

Pingitore R, Squartini F
Istituto di Anatomia Patologica, Scuola Medica, Via Roma 57, 56100 Pisa, Italy
Tumori; 68(3):199-203 1982

The morphologic patterns of mammary tumors induced by milk-transmitted C3H and RIII murine mammary tumor viruses (MuMTVs) in BALB/c hosts infected by foster nursing were investigated further and compared taking into account several tumor and host variables. Comparison of BALB/cfC3H and BALB/cfRIII mammary tumors under identical tumor and host conditions showed highly significant differences in subgross morphology and histologic structure. Differences in cytology were also observed. Data suggest that mammary tumor morphology in high cancer strain mice is controlled by the causative MuMTV. (Author abstract) (14 Refs)

11. FORMATION OF DUCT-ALVEOLAR STRUCTURES AND NEW TYPES OF TUMORS BY A PREGNANCY-DEPENDENT MOUSE MAMMARY TUMOR (TPDMT-4) IN VIRGIN MICE.

Matsuzawa A, Kaneko T, Ikeda Y, Yamamoto T
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Gan; 73(3):372-376 1982

TPDMT-4 tumors showed significant growth in pregnant mice but not in virgins. Tumor pieces at transplant generation 14 were implanted into the gland-free (right) and the intact (left) fat pads in virgin mice and followed over a 1-yr period. The transplants formed outgrowths similar to normal mammary glands in the cleared fat pads. The outgrowths were hyperactive when compared with host glands and varied from one mouse to another in extent of development. In contrast, they did not outgrow and remained as traces among host glands in the intact fat pads. Tumors developed 41 and 32 wk after implantation in the right and the left pads, respectively, in one of 18 mice. The tumor from the cleared fat pad was an ovarian-sensitive pale cell carcinoma, and contained estrogen receptors (ER) but not progesterone receptors (PR). That from the intact fat pad was a type B carcinoma which was ovarian-dependent and contained both ER and PR at levels comparable to those of the parent tumor. (Author abstract) (16 Refs)

12. COMPARISON OF MAMMARY TUMORIGENESIS BETWEEN LITTERS IN RELATION TO MAMMARY TUMOR VIRUS ANTIGENIC EXPRESSION IN THE MILK OF C3H/HE MICE.

Nagasawa H, Nakajima Y, Morimoto J, Imai S, Tsubura Y
Experimental Animal Res. Lab., Meiji Univ., Tama-ku, Kawasaki,, Kanagawa 214, Japan
Life Sci; 31(1):83-88 1982

As a possible step to estimate the relationship between mammary tumor virus (MTV) and mammary tumorigenesis in mice, MTV antigenic expression in mother's milk and spontaneous mammary tumorigenesis in their daughters were compared between the first, the second and the third litters of the highly inbred strains of C3H/He mice with low mammary tumor incidence. While MTV antigenic expression was detected in all undiluted samples at each litter by immunodiffusion test, the amount of antigen as measured by the single radial immunodiffusion method was increased with increasing litter numbers. On the other hand, the development of preneoplastic mammary hyperplastic alveolar nodules was different little between litters and mammary tumor incidence by 13 mo of age was very low with no difference in all litters. The pattern of estrous cycles and plasma prolactin level were also similar in each litter. The results suggest that spontaneous mammary tumorigenesis in mice is not always affected quantitatively by the amount of MTV when endocrine and genetical conditions are similar. (Author abstract) (19 Refs)

13. FIBRIN CLOT RETRACTILE (FCR) ACTIVITY OF FIBROBLAST-LIKE CELLS FROM NORMAL INDIVIDUALS AND CANCER PATIENTS.

Curatolo L, Borgia R, Donati MB, Morasca L
Istituto di Ricerche Farmacologiche 'Mario Negri', Via Eritrea 62, 20157 Milan, Italy
Cell Biol Int Rep; 6(6):609-618 1982

Changes in fibrin clot retractile activity (FCRA) were studied under standardized conditions in fibroblasts from healthy donors of various ages, subjects with genetic abnormalities, and various types of cancer patients. Cells were serially cultured in Eagle's minimum essential medium on Hank's balanced salt soln plus 10% bovine serum. Cells usually were tested at least 10 passages before the end of the culture. The test system involved retraction of fibrin clots formed by clotting a mixture of test cells and platelet-free plasma with thrombin. A constant concentration of 1 x 10(6) cells/ml was used and results were reported 24 hr after incubation of the clot at 37 C. Cells with a finite replicative life still had high FCRA late in their lifespan. FCRA was completely lost in cells with an infinite replicative lifespan. FCRA was sometimes reduced in fibroblasts from the skin of patients with colorectal adenomatosis and a Kirsten sarcoma virus infected line. A group of human fibroblasts from cancer patients was unable to induce FCRA. No difference was found in FCRA of cells from normal embryos or adults. The role of fibrin in relation to the spread of cancer is discussed. (22 Refs)

VIRUS REPLICATION AND EXPRESSION

14. INTERFERENCE GROUPING OF MURINE LEUKEMIA VIRUSES: A DISTINCT RECEPTOR FOR THE MCF-RECOMBINANT VIRUSES IN MOUSE CELLS.

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Virology; 120(1):251-257 1982

Fourteen different isolates of mink cell focus-inducing (MCF) murine leukemia viruses (MuLV) were characterized with respect to viral interference on NIH/3T3 cells. I assayed viral interference by measuring the reduction in focus formation by murine sarcoma virus pseudotypes on cells chronically infected with MuLV. Although the MCFs interfered with each other in all combinations tested, there was no significant cross-interference between MCF and ecotropic MuLVs. These results imply that MCFs and ecotropic MuLVs enter NIH/3T3 cells via different receptors. Using a recombinant constructed in vitro by C Holland and N Hopkins, I also found that the receptor specificity of MuLV is determined by sequences to the 5' side of 7.7 kbp (measured from the 5' end of the provirus). The distinct receptor specificity of MCFs suggests that they may be recombinants in which the nonecotropic parent is not xenotropic MuLV, as originally proposed, but rather endogenous env sequences which are not part of nondefective viral genomes. The MCF receptor specificity may be encoded directly by these sequences. I also suggest that interference may have a profound effect on the dynamics of viral replication in vivo. (Author abstract) (43 Refs)

15. PRODUCTIVE INFECTION OF EMBRYONAL CARCINOMA CELLS WITH ECOTROPIC MOUSE TYPE C VIRUSES AND SUBSEQUENT ARREST OF DIFFERENTIATION.

Levy JA, Jakob H, Paulin D, Kelly F, Chermann JC, Jacob F
Dept. Medicine, Cancer Res. Inst., Univ. California Sch. Medicine, San Francisco, CA, 94143
Virology; 120(1):157-170 1982

Certain lines of mouse embryonal carcinoma (EC) cells, while morphologically undifferentiated, were productively infected with strains of mouse ecotropic Type C viruses (MuLV). They could not be infected with xenotropic MuLV. This ability to circumvent the reported resistance of EC cell lines to ecotropic MuLV infection appeared related to the use of a high-input multiplicity of infection (moi). Results with a variety of EC lines demonstrated differences in their resistance to MuLV infection. In some cell lines, addition of 3-10 infectious viruses/cell gave rise to productive infections. In others, moi values as high as 100-1,000 were required. In the productively infected EC cell line, PCC7-S AzaR1, normal differentiation into nerve cells was blocked. The mechanism for this influence of MuLV on the differentiation process is not known, but it only occurred when a large number of cells was releasing virus. These results suggest that this inhibition of differentiation is mediated by virus particles budding from the cell surface. (Author abstract) (38 Refs)

16. DIVERSE XENOTROPIC VIRUS EXPRESSIONS IN TWO NZB MOUSE BREEDING LINES THAT DIFFER IN CHROMOSOME BREAKAGE.

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JNCI; 68(6):951-955 1982

Two breeding lines of the NZB/Bl mouse strain, which was originated from Bielschowsky's stock and maintained as a conventional inbred colony since 1963, were developed by selective matings according to chromosome breakage incidence in bone marrow cells. These breeding lines were used because they represent an interesting experimental model, since they differ in the manifestations of the autoimmune process and the incidence of lymphomas. The present study showed that embryos from both breeding lines differed in the expression of the xenotropic type C RNA virus, characteristic of NZB mice. All 17 cultures initiated with embryos from the line showing high chromosome breakage (HB) had positive reverse transcriptase (RT) reactions after cocultivation with an indicator cell line (SIRC). On the contrary, only 3 of the 22 embryos from the line showing low chromosome breakage (LB) had RT activity at late passages (7-10). The chromosome studies done on these embryo cultures showed highly significant differences in the chromosome breakage incidence for the 2 breeding lines [10.6 and 20.5% of cells with aberrations for LB and HB embryos, respectively (P less than 0.001)] (Author abstract) (22 Refs)

17. RADIOIMMUNOASSAY FOR MAJOR EXTERNAL GLYCOPROTEIN OF MURINE MAMMARY TUMOR VIRUS.

Chiplunkar SV, Karande KA
Dept. Immunology, Cancer Res. Inst., Bombay 400 012, India
Indian J Exp Biol; 20(2):121-125 1982

A radioimmunoassay assay is described in which highly purified intact murine mammary tumor virus (MuMTV) virions from the expressed milk of strains C3H(Jax) and ICRC mice were externally labeled with 125I in the presence of lactoperoxidase. Heterologous polyvalent antisera prepared against disrupted virions were used for immunoprecipitation. Sodium dodecyl sulfate polyacrylamide electrophoresis showed that both iodinated virions migrated as a single peak with an estimated mol wt of 49,000 daltons. This peak corresponds to the previously described major membrane glycoprotein (gp 49) of MuMTV. Competition radioimmunoassays using antisera to MuMTV C3H and MuMTV ICRC with their respective labeled virions were shown to be specific for MuMTV antigens. Tissue extracts of C57BL liver and lactating mammary gland, ICRCf liver, swiss mouse milk plasma and fetal calf serum proteins did not compete in the assay. The addition of 4 ug of unlabeled MuMTV ICRC completely inhibited the binding of anti-MuMTV ICRC serum to 125I-labeled MuMTV ICRC. Large amounts of gp 49 were found in tumor extracts (940-3,937 nanog/mg) and sera (160-680 nanog/ml) of C3H and ICRC tumor-bearing mice. The assay can detect 3 nanog of antigen and is highly reproducible. (29 Refs)

18. JAPANESE QUAIL EMBRYO CELL LINE PERSISTENTLY INFECTED WITH ERYTHROBLASTOSIS VIRUS.

Yoshikawa Y, Bauer H, Reinacher M, Ziemiecki A
Lab. Animal Res. Center, Inst. Medical Science, Univ. Tokyo, Shirokanedai, Minato-ku, Tokyo 108, Japan
Jpn J Exp Med; 52(2):75-87 1982

The characteristics of Japanese quail embryo (QE) cell line QERC-31F (F) and released virus were examined in both virological and cytological aspects. The virus failed to transform QE cells but induced erythroblastosis by injection into neonatal quails. Injection of F cells in neonatal quails resulted in solid tumors diagnosed as undifferentiated sarcoma. Antiserum to chicken RBC histone V fraction stained the nucleus of F cells. The study suggests that the F cell line maintains characteristics of the erythroblast and possibly produces avian erythroblastosis virus as well as helper virus of subgroup A. (11 Refs)

19. REACTIVATION OF LATENT FELINE LEUKAEMIA VIRUS INFECTION.

Rojko JL, Hoover EA, Quackenbush SL, Olsen RG
Dept. Veterinary Pathobiology, Ohio State Univ., 484 W. 12th Ave., Columbus, OH, 43210
Nature; 298(5872):385-388 1982

Reactivation of latent feline leukemia virus (FeLV) from myelomonocytic and lymphoid cells of cats immune to FeLV, cats bearing FeLV-negative tumors, and kittens congenitally exposed to FeLV is reported. Self-limiting (regressive) FeLV infection was established in adult specific pathogen-free cats. At 16-20 wk after exposure, femoral bone marrow cells, mesenteric lymph node cells, peritoneal macrophages, and peripheral blood mononuclear leukocytes (PBML) were collected. High titers of FeLV were reactivated following isolation and in vitro propagation of marrow from 8/10 FeLV-immune cats, but not from four FeLV-naive cats. It was shown that refractoriness to retroviral replication accompanied differentiation of feline myelomonocytic progenitor cells. In samples from two cats with FeLV-negative lymphosarcoma of the lymph nodes, virus was reactivated only from cultured marrow cells, not blood or tumor cells. Two regressor females were mated with two regressor males and produced two litters of five kittens with evidence of congenital FeLV infections; both females had been re-exposed by a single ip dose of FeLV during the first wk of gestation. Infectious virus was expressed in cultured marrow from three kittens, cultured thymus of two kittens, and freshly isolated as well as cultured, liver hematopoietic cells from one fetal kitten. The in vitro and in vivo effect of corticosteroids on latent FeLV infections was studied; three of five cats contained reactivated FeLV, while two remained persistently viremic 135 days after initiation of treatment. Thus, FeLV persists as an integrated latent infection in marrow myelomonocytic precursor cells and T lymphocytes and can be reactivated by liberation from host immunological controls. (35 Refs)

20. STUDY OF ENDOGENOUS ONCORNA VIRUS ACTIVATION FOLLOWING TREATMENT WITH N-METHYL-N-NITROSOUREA IN MURINE THYMUS.

Pinter A, Csik M, Borzsonyi M, Torok G, Vincze I, Surjan A
Orszagos Kozegeszsegugyi Intezet, Budapest, Hungary
Magy Onkol; 26(2):147-151 1982

Activation of endogenous oncorna virus in thymus glands of female BDF1 mice treated with single doses of N-methyl-N-nitrosourea (MNU: 80 mg/kg ip) was studied. An initial reduction of the absolute and relative weights of the thymus was followed by a slight increase to above the respective normal values by day 41 after MNU treatment. Endogenous virus activation was not observed by the infectious center test during the immunosuppressive (24-72 hr after treatment) and regenerative phases (11 and 26 days after treatment). Increasing titers of ecotropic endogenous mouse leukemia virus were observed in the thymus cells of the animals killed 41 days after MNU treatment (prelymphomatous stage). The findings indicate that the appearance of endogenous viruses during the prelymphomatous stage might play a role in the pathogenesis of MNU-induced lymphomas. (17 Refs) (In HUN)

21. ENDOGENOUS RETROVIRUSES OF MICE AND CHICKENS.

Steffen DL, Robinson H
Worcester Foundation Experimental Biology, 222 Maple Ave., Shrewsbury, MA, 01545
Curr Top Microbiol Immunol; 98:1-10 1982

Characteristics of murine leukemia viruses (MLV) found in laboratory mice and avian leukosis viruses (ALV) found in chickens are reviewed. These viruses occur as endogenous retroviruses (ERV) in the host animals. ALV proviruses constitute one closely related family. MLV constitute two or more families. ALV occur as 0-5 copies in the DNA of chickens, while MLV are represented by a larger number of copies. ALV are relatively easy to analyze structurally; analysis of MLV proviruses is more complicated, and therefore fewer MLV have been analyzed. Five structural classes of ALV have been identified; three of these classes have been identified among MLV. ERV occur throughout the host genome, indicating that infection is the source of ERV. The number of copies of endogenous proviruses in the host genome may increase over time; this increase probably results from reinfection. Endogenous proviruses may genetically complement or recombine with exogenous or endogenous infecting viruses. Expression of endogenous proviruses is apparently controlled by methylation of DNA. Chicken and mouse hosts display resistance to ERV. Resistance at the level of adsorption and penetration evidently results from loss of surface receptors by the host cell. Resistance may also develop at a level after penetration. Current evidence suggests that the most evolved proviruses are the most widely distributed; xenotropic MLV are the most highly selected, while ALV are at an intermediate stage of selection, and endogenous ecotropic MLV are the least evolved. (25 Refs)

GENETICS

22. INFLUENCE OF B LOCUS ON AVIAN VIRAL INDUCED TUMORS.

Cauchy L, Dambrine G, Coudert F
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Bull Cancer (Paris); 69(2):194-198 1982

Since early in the century Avian Cancers were described as induced by viruses which later were known of DNA and RNA types. The susceptibility of birds was found different according to the genetic lines of the chickens and specially to the B locus blood group. since the B locus of birds was strongly associated with the Major Histocompatibility Complex (MHC) it was of interest to review the last reports on the influence of the B locus on viral induced tumors. In Marek's Disease due to a DNA virus (Herpes type) the B21 allele expresses the greater resistance compared with other B alleles although non-B factors could be involved as demonstrated with the lymphocyte factor Ly-4. The possible mechanisms of the influence of B locus on the resistance against Marek's Disease are discussed. The tumors induced by RNA viruses (Avian Leucosis Sarcomas) develop or regress following genetic characters closely related to MHC. Differences of resistance exist between B alleles. Complementary genes should be present to fully express the resistance. The relationship between MHC-B locus and resistance to tumors stimulates the actual assays. Since a number of parameters remain still unknown further research should be done in order to evidence the involved mechanisms of the resistance. (Author abstract) (26 Refs) (In FRE)

23. GENETIC CONTROL OF MURINE LEUKEMIAS INDUCED BY MOLONEY VIRUS.

Debre P, Gisselbrecht S, Boyer B, Levy JP
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Bull Cancer (Paris); 69(2):178-187 1982

The genetic control of leukemias was established in mice of different inbred strains inoculated with Moloney leukemia virus M-MuLV. To characterize the different steps of the host virus relationship, the degree of viremia, the appearance of leukemia, organ involvement, and the surface phenotype of leukemic cells were determined in individual mice. Immunological responses of those mice were studied by comparing the antibody production against virus or infected cells, and cytolytic T cell (CTL) responses. The results demonstrate that: (a) the viremia was controlled by H-2 and non H-2 genes. Three Rmv H-2 genes were located in the I and D or T region of the MHC. These genes behave like immune response genes controling the specific antiviral antibody production. D region Ir gene(s) also controlled the CTL but apparently differed from the Rmv genes. In addition to H-2 genes other gene(s) mapped outside the complex affected the virus production; (b) non H-2 genes which were not involved in viremia control, were determinant in the induction of malignancies since some sensitive strains never became leukemic despite high level of viremia; (c) the anatomical type of Moloney virus induced leukemias varied according to the non H-2 background since Thymus or spleen involvement differed in B10 and BALB congenic mice; (d) in a given inbred strain, the leukemia arising in different animals frequently expressed different phenotypes. It can be concluded that Moloney virus induced leukemia is a multistep process. H-2 Ir genes control the antiviral-antibody responses. However, the mode of action of other non H-2 genes is still unknown. (Author abstract) (25 Refs) (In FRE)

24. SURFACE ANTIGEN EXPRESSED IN HEMATOPOIETIC CELLS DERIVED FROM FV-4 MOUSE STRAINS.

Yoshikura H, Odaka T
Dept. Microbiology, Univ. Tokyo, P. O. Box Hongo, Tokyo 113, Japan
JNCI; 68(6):1005-1009 1982

Fv-4 locus controls the susceptibility of mice to ecotropic murine leukemia virus. Antiserum against Fv-4r/s mice with BALB/c background was raised in inbred BALB/c mice. In the complement-dependent cytotoxicity test, the antiserum killed the hematopoietic cells derived from Fv-4r/- mice but not those from Fv-4s/s mice, and the genetic cross experiments located the locus controlling the expression of the target molecule of the antibody in the close vicinity of Fv-4. In addition, the antigenic expression of the exogenously infecting MuLV suppressed the expression of the target molecule of the antiserum. The expressions of these two antigens appear to compete with each other on the cell surface. (Author abstract) (21 Refs)

IMMUNOLOGICAL STUDIES

25. ISOLATION OF MALIGNANT AND FUNCTIONAL LY 1+ T-CELL CLONES FROM B-CELL LYMPHOMAS.

Reinisch CL, Sing AP, Waldron JA, Kemp JD
Dept. Comparative Medicine, Tufts Univ. Sch. Veterinary Medicine, Boston, MA, 02111
Nature; 298(5870):176-178 1982

A unique model of a murine sarcoma virus (MSV)-induced B-cell lymphoma which is closely associated with a population of pre-malignant or malignant helper T cells was discovered in selected C57BL/6(B6) mice. Three-wk-old mice were injected im with 6 x 10(3) focus-forming units of murine sarcoma-murine leukemia virus (MSV). Those that developed a palpable tumor after 21 days were observed for more than 2 yr, during which time 15/17 developed mesenteric lymphadenopathy. Cell suspensions prepared from an enlarged mesenteric lymph node were injected into normal mice; all developed splenic and lymph node tumors 3 mo later. The transplantable tumor, called STC, produced progressive expansion of the splenic white pulp and of the paracortical and medullary cord areas of lymph nodes. The tumor infiltrates consisted mostly of small lymphocytic cells with varying degrees of plasmacytoid differentiation. Frequent PAS-positive cytoplasmic and intranuclear inclusions were present. An attempt to transfer STC with B cells resulted in Ly 1+ T cells instead; eleven clones produced the same way had the phenotype Thy 1.2+ (monoclonal antibody 30 H12), Ly 1+, Ly 2-. Doses of one clone injected into B6 mice resulted in rapid death due to immunoblastic T-cell sarcoma, morphologically distinct from the plasmacytoid lymphocytic lymphomas induced by MSV, STC, or B cells. Reverse hemolytic plaque assay demonstrated the ability of these clones to enhance Ig secretion by plasma cells in the absence of antigen. (14 Refs)

26. CELL-MEDIATED IMMUNITY TO MOUSE MAMMARY TUMOR VIRUS ANTIGENS BY PATIENTS WITH HYPERPLASTIC BENIGN BREAST DISEASE.

Cannon GB, Barsky SH, Alford TC, Jerome LF, Tinley V, McCoy JL, Dean JH
Immunotoxicology Section, Litton Bionetics, Inc., 5516 Nicholson Lane, Kensington, MD, 20795
JNCI; 68(6):935-943 1982

Peripheral blood leukocytes of patients with preoperative breast cancer, benign breast disease, and benign gynecologic disorders and normal healthy females were tested, as blind coded specimens, with murine mammary tumor virus (MuMTV) antigens in the direct and indirect leukocyte migration inhibition (LMI) assays. The incidence of reactivity by patients with breast cancer was low. (From 5 to 35% breast cancer patients reacted, depending on which group of control individuals they were compared to and what antigen was used.) Nonparametric analyses showed no differences between control groups (normal donors and patients with gynecologic disorders) and breast cancer patients with either assay. However, there was a significant difference between benign breast disease patients with hyperplasia and (1) benign breast disease patients without hyperplasia (p less than 0.03) and (2) patients with gynecologic disorders (p less than 0.040) in the direct assay when it was performed blindly with the gp52 antigen. Patients with hyperplasia (benign breast disease as well as breast cancer) had a higher incidence of enhanced migration in the indirect test than breast disease patients without hyperplasia. The enhanced migration to the MuMTV was correlated to enhanced migration to a 3-M KCl extract of the breast cancer cell line MCF-7 in simultaneous tests. Thus the LMI assays with MuMTV antigens do not appear valuable in breast cancer diagnosis, but they may help to identify a small group of benign breast disease patients whose breast pathology is thought to be associated with a high risk for developing breast cancer. (Author abstract) (20 Refs)

27. INHIBITION OF CONCANAVALIN A RESPONSE DURING OSTEOPETROSIS VIRUS INFECTION.

Price JA, Smith RE
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Cancer Res; 42(9):3617-3624 1982

Infection of animals with oncogenic viruses frequently leads to an immunosuppressed state. We have examined immunosuppression induced by an avian osteopetrosis virus, myeloblastosis-associated virus of subgroup B inducing osteopetrosis [MAV-2(O)], and our results suggest that this virus induces immunosuppression by a novel mechanism. Lymphoid cells from osteopetrotic chickens did not respond to a wide dose range of concanavalin A (Con A) over a wide cell density range. Failure to undergo blastogenesis was not due to a lack of Con A-binding sites, since 125I-labeled Con A bound to lymphocytes from infected and uninfected chickens. Infected lymphocytes failed to respond to uninfected chickens. Infected lymphocytes failed to respond to sodium metaperiodate stimulation, indicating that failure of blastogenesis was not due to a blockage of Con A receptor sites. MAV-2(O) infection of chicks 8 days of age resulted in a transient immunosuppression which appeared 1 to 2 wk after infection. Cell-mixing experiments showed that MAV-2(O)-induced immunosuppression was not attributable to suppressor cells. In contrast, adherent cells from normal lymphoid preparations restored mitogenicity to lymphocytes from MAV-2(O)-infected animals. Adherent cells were present in the spleen and peripheral blood lymphocytes of MAV-2(O)-infected chickens in numbers comparable to those of the uninfected animal, and both sets of cells contained Fc-dependent phagocytic activity and nonspecific esterase. Peritoneal exudate cells were elicited from osteopetrotic and normal chickens in similar numbers. We conclude that MAV-2(O) induces immunosuppression by interfering with an accessory function of macrophage-like adherent cells. (Author abstract) (55 Refs)

28. T HELPER CELLS IN IMMUNE MICE AMPLIFY THE PRIMARY ANTITUMOR CYTOTOXIC RESPONSE.

Yu AS, Bernstein ID
Pediatric Oncology Program, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
J Immunol; 129(2):856-859 1982

In this report we examine the influence of splenic helper cells in the primary cytotoxic T lymphocyte (CTL) response against syngeneic murine leukemia virus-(MuLV) induced tumor cells. We identify an Lyt-1+ 800 R radiation-resistant helper T cell that will amplify the in vitro generation of CTL against syngeneic tumor cells from nonimmune spleen cells. (Author abstract) (25 Refs)

29. ESTABLISHMENT OF FUNCTIONAL, ANTIGEN-SPECIFIC T CELL LINES BY RADLV-INDUCED TRANSFORMATION OF MURINE T LYMPHOCYTES.

Ricciardi-Castagnoli P, Rabbiati F, Barbianti E, Doria G, Adorini L
No affiliation given
Curr Top Microbiol Immunol; 100:89-96 1982

Radiation leukemia viruses (RadLV) were produced by exposing C57Bl/Ka mice to radiation. The RadLv were isolated from the resulting thymomas. T-cell lines containing the viruses were established that secrete antigen-specific and maintain functional activity in spite of undergoing transformation. RadLV in the T-cell lines are endogenous leukemogenic retroviruses with high oncogenic capacity. RadLV induce neoplastic transformation in target tissues including bone marrow, spleen, thymus, and fetal liver. No transformation of cells of B lineage has not been reported. Antigen-specific T lymphocytes can be infected with RadLV in vitro; transformation occure, however, only if the cells are maintained under conditions which support cellular proliferation. Cells bearing the H-2b haplotype or the Fv-1bb gene are the most susceptible to infection with RadLV; other cell types tend to be resistant to RadLV. Antigen-specific, functional T-cell lines are established by enriching specific T-cells and then infecting them with RadLV. The infected cells are then injected into sublethally irradiated mice, and tumors are allowed to develop. Individual cell lines are produced by cloning. Cells are selected for cloning by means of phenotypic and functional assays. Products of a T-cell line specific for hen egg-white lysozyme (HEL) have been characterized. Since the HEL-specific cells do not suppress a structurally related lysozyme, the specificity of the cells is quite narrow. The specificity is determined by the N-terminal, C-terminal peptide in the HEL molecule. Suppressor activity is restricted by genes located in the H-2 complex and requires identity of the I-J region of the H-2 complexes of the cell factor and its target. (16 Refs)

30. PRODUCTION OF MACROPHAGE-ACTIVATING FACTOR BY T LYMPHOCYTE CLONES AND CORRELATION WITH OTHER LYMPHOKINE ACTIVITIES.

Kelso A, Glasebrook AL, Kanagawa O, Brunner KT
Dept. Immunology, Swiss Inst. Experimental Cancer Res., 1066 Epalinges, Switzerland
J Immunol; 129(2):550-556 1982

The production of macrophage-activating factor (MAF) by antigen-stimulated murine T lymphocyte clones has been compared with their cytolytic function and release of other lymphokines. MAF activity was measured by the capacity of peptone-induced peritoneal exudate cells or bone marrow-derived macrophages to lyse 51Cr-labeled tumor cells after incubation with supernatant from the stimulated T cells and a nonactivating, amplifying dose of lipopolysaccharide. Of 72 clones generated against H-2, Mls, H-Y, or Moloney leukemia virus-associated antigens, 68 were found to produce detectable quantities of MAF. Release of MAF by clones (1) occurred within 1 to 12 hr of exposure to antigen, (2) required stimulation with cells of the relevant antigenic specificity, and (3) could also be induced by concanavalin A, indicating that the cloned cells were the source of the activity. The capacity of a clone to produce MAF was independent of its antigenic specificity, cytolytic activity, or ability to produce interleukin 2 or granulocyte-macrophage colony-stimulating activity. In contrast, production of interferon and MAF was not dissociated for any of the clones tested. (Author abstract) (42 Refs)

31. DELAYED TYPE HYPERSENSITIVITY RESPONSES TO RADIATION LEUKEMIA VIRUS VARIANTS.

Strassmann G, Haran-Ghera N
Dept. Chemical Immunology, Weizmann Inst. Sci., Rehovot 76100, Israel
Cell Immunol; 70(1):196-199 1982

DTH responses were evaluated in different strains of mice shown to be resistant or sensitive to leukemogenesis by the radiation leukemia virus variants A-RadLV and D-RadLV. A significant response was observed only in the H-2 complex-linked resistant haplotypes to RadLV leukemogenesis. The DTH response could be transferred by immune cells of mice resistant to the appropriate RadLV variant. Thus, an inverse relationship between the leukemogenic activity of the virus and its immunization ability expressed by DTH response was demonstrated in different mouse strains. (Author abstract) (10 Refs)

32. CIRCULATING IMMUNE COMPLEXES, ANTIGENS, AND ANTIBODIES RELATED TO THE MURINE MAMMARY TUMOR VIRUS IN C3H MICE.

Dong ZW, Witkin SS, Fernandes G, Sarkar NH, Good RA, Day NK
(c/o Day), Oklahoma Medical Res. Foundation, 825 N.E. 13th St., Oklahoma City. OK, 73104
J Immunol; 12[illegible]872-876 1982

A comparative study was performed to measure levels of free antibody to MuMTV, MuMTV membrane antigen (gp52), and antigen-antibody complexes in sera of mammary tumor-bearing and age-matched non-tumor bearing C3H/Bi mice. Approx 90% of these mice spontaneously develop breast cancer. Levels of MuMTV antibody and C3-containing circulating immune complexes (CIC) were highest in the sera of the mice without overt evidence of breast cancer. MuMTV gp52 antigen was present in higher concentrations in the sera of mice with overt breast cancer. Fractionation of the sera on sucrose gradients followed by analysis for CIC confirmed that levels of C-containing CIC were lower in sera from mice with tumors than in nontumor bearers. The CIC were, however, of smaller size in sera of tumor-bearing mice. When the sera were assayed for CIC by an assay in which C binding does not compete with binding of CIC to the sperm, the levels of these small-sized CIC in sera of mice with breast cancer were now comparable to CIC levels in nontumor-bearing mice. MuMTV antibody was located in both 7S and high mw regions of the gradients. To determine whether the CIC contained MuMTV antigen, the CIC were bound to bull sperm Fc receptors and assayed for reactivity with monospecific goat anti-gp521gG. Significantly higher levels of reactivity to anti-gp52 were detected in CIC from C3H mice than in CIC from sera of age-matched AKR mice with or without leukemia or from MRL/MpJ-Ipr/Ipr mice. These data indicate that there is a shift from MuMTV antibody excess to MuMTV antigen excess and from larger C-fixing CIC to smaller non-C-fixing CIC after appearance of overt breast cancer in C3H mice. (26 Refs)

33. SOMATIC CELL HYBRIDIZATION BETWEEN BOVINE LEUKEMIA VIRUS-INFECTED LYMPHOCYTES AND MURINE PLASMA CELL TUMORS: CELL FUSION STUDIES WITH BOVINE CELLS.

Davidson I, Katzav S, Ungar-Waron H, Eshhar Z, Haimovich J, Trainin Z
(c/o Trainin) Dept. Immunology, Kimron Veterinary Inst., Bet Dagan 50250, Israel
Mol Immunol; 19(7):893-899 1982

Hybridization of peripheral blood lymphocytes from bovine leukemia virus-infected cows with murine myeloma cells resulted in the generation of hybrid cells secreting immunoglobulins composed of various combinations of heavy and light chains of both bovine and murine Ig origin. Some hybrid cells derived from the light-chain producer, but non-secretor murine myeloma NS1 cell line, secreted IgM molecules composed of bovine mu-chain linked to bovine and/or murine light chains. Other hybridomas secreted mouse and bovine light-chain dimers and/or monomers, or failed to secrete any Ig polypeptide chain whatsoever. Immunoglobulins secreted by hybridomas obtained upon hybridization of bovine cells with the IgG-secreting murine myeloma P3X63 cell line, contained bovine mu-chain in one of the seven hybridomas obtained, and bovine light chain in two of them. All the cell lines secreted murine light- and gamma-chains. (Author abstract) (27 Refs)

34. EXPRESSION OF TYPE C VIRAL GLYCOPROTEINS ON P815 CELLS: HIGHER EXPRESSION OF MR 70,000 GLYCOPROTEIN-CONTAINING GLYCOPROTEIN ON IMMUNOGENIC VARIANTS.

Jacquemin PC
Brussels Branch, Ludwig Inst. Cancer Res., 74 avenue Hippocrate, UCL 74.59, B-1200 Brussels, Belgium
Cancer Res; 42(9):3828-3836 1982

Cells from P815 mastocytoma, a methylcholanthrene-induced tumor, were investigated for the presence of Type C viral proteins on their surface. Little or no precipitation of purified Rauscher murine leukemia virus Mr 70,000 glycoprotein was observed with sera of mice immunized with P815 cells. However, a significant precipitation was obtained with sera from syngeneic or allogeneic mice immunized with P815 tumor cell variants obtained by mutagenesis. This difference was not detected when the sera were tested for precipitation of a pure Rauscher murine leukemia virus Mr 30,000 protein. The positive sera also precipitated a Mr 90,000 glycoprotein present on the membrane of all P815 cells. This glycoprotein was shown to contain endogenous ecotropic murine leukemia virus Mr 70,000 glycoprotein. On the membrane, a separate glycoprotein with a mol wt of 90,000 containing gag gene products was also detected with a panel of reference antibodies. The level of glycoprotein containing Mr 70,000 glycoprotein on the cell membrane of the mutagenized cell variants was higher compared to the original P815 cells. The level of expression of the glycosylated gag precursor was the same on the original P815 cells and on the mutagenized cell variants. (Author abstract) (29 Refs)

35. CHARACTERIZATION OF AN ANTIGEN ASSOCIATED WITH THE MAREK'S DISEASE LYMPHOBLASTOID CELL LINE MSB-1.

Ross LJ
Houghton Poultry Res. Station, Huntingdon, Cambs. PE172DA, England
J Gen Virol; 60(part2):375-380 1982

A Marek's disease lymphoblastoid cell line (MSB-1) has been analyzed by immunoprecipitation for expression of tumor-associated antigen, Marek's disease virus (MDV)-specific antigens and antigens specific to avian leukosis-sarcoma viruses. Rabbit antisera raised against two independently derived cell lines after extensive absorption with normal chick cells reacted with a polypeptide of mol wt 40,000 (40K) in extracts of MSB-1 cells. The 40K polypeptide was not present in myeloblasts or in chick embryo fibroblasts (CEF) infected with MDV and did not react with antiserum raised against normal chicken thymus antigens. The possibility that the 40K polypeptide is a tumor-associated antigen is discussed. Seven MDV-specific antigens were noted in infected CEF (mol wt 110K, 100K, 80K, 70K, 50K, 35K and 32K) but none of these was detected in MSB-1 cells. The avian leukosis-sarcoma group-specific antigen P27gag and its precursor Pr76gag were not found in MSB-1 cells, confirming that expression of mature gag protein is not required for transformation by MDV. However, two polypeptides of unknown origin and function (mol wt 180K and 110K) were precipitated from MSB-1 cells with a rabbit anti-Rous sarcoma (Schmidt-Rupin, subgroup D) antiserum. (Author abstract) (17 Refs)

36. ANTIGENIC AND CHROMOSOMAL CHANGES IN THYMUS AND SPLEEN OF BALB/MO MICE DURING LEUKEMOGENESIS.

Asjo B, Fenyo EM, Spira J
Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm, Sweden
Leuk Res; 6(3):413-419 1982

Correlation between the amplification of the Moloney murine leukemia virus (M-MuLV) and appearance of M-MuLV induced cell surface antigen, MCSA, on thymus cells was studied in Balb/Mo mice. Production of infectious virus in the preleukemic mice was accompanied by the appearance of viral p30 antigen on the surface of thymus cells. All organs of Balb/Mo mice were negative for MCSA up to 40 days. Thereafter occasional thymuses contained a low fraction of MCSA-positive cells. Thus, Balb/Mo mice differed from mice neonatally inoculated with M-MuLV since the amplification of the viral genome was not accompanied by the appearance of

MCSA on thymus cells. Mice mainly developed lymphomas with two distinct clinical manifestations. One type was characterized primarily by enlargement of spleen and lymph nodes, and the other by enlargement of thymus with eventual infiltration of peripheral lymphatic organs. Leukemia latency varied between 3-10 mo and was not correlated with any particular type of lymphoma. Thymus cells were often MCSA positive while spleen cells of the same animal were MCSA negative. Based on the antigen patterns of thymomas and lymphomas, Balb/Mo lymphoma mice were more often negative for MCSA (68%) than mice receiving M-MuLV at birth (40%). The majority of thymus cells was MCSA positive while the spleen was MCSA negative. No correlation between the antigen expression and chromosome constitution could be observed. Amplification of the M-MuLV genome in young Balb/c mice was not accompanied by the appearance of MCSA on thymus cells. Results suggested that MCSA is related to a virus activated in a minority of Balb/Mo mice during the late phase of leukemogenesis. (14 Refs)

37. IMMUNE STIMULATION OF SENSITIZED CHICKEN LYMPHOCYTES BY AVIAN RETROVIRUS PROTEINS.

Wainberg MA, Israel E
Lady Davis Inst. for Medical Res., Sir Mortimer B. Davis Jewish General Hosp., 3755 Cote Sainte Catherine Road, Montreal Quebec, H3T 1E2, Canada
J Gen Virol; 60(part2):391-395 1982

Peripheral blood lymphocytes of chickens bearing tumors induced by avian sarcoma virus can be specifically stimulated to divide by the crude culture fluids of virus-infected cells. In this communication, we show that relevant antigenic activity apparently resides in each of the internal virus proteins p15 and p27. The ability of infectious culture fluids to be mitogenic for sensitized lymphocytes is greatly reduced following treatment with antibodies specific for either total avian myeloblastosis virus (AMV) protein or for p27. (Author abstract) (14 Refs)

38. SPECIFIC IMMUNOTHERAPY COMBINED WITH WHOLE BODY IRRADIATION OF BALB/C MICE BEARING MOLONEY MURINE SARCOMA VIRUS-INDUCED PRIMARY TUMORS.

Kimura H, Yamaguchi Y, Fujisawa T
Dept. Surgery, Inst. Pulmonary Cancer Res., Sch. Medicine, Chiba Univ., Inohana 1-8-1, Chiba 280, Japan
Gan; 73(3):446-453 1982

Adoptive transfer of lymphocytes was performed into mice bearing progressor Moloney murine sarcoma virus (M-MSV)-induced primary tumors. Lymphocytes from mice immunized against M-MSV (designated as immune lymphocytes, IL) inhibited tumor growth when transferred before the virus injection. However, the same lymphocytes were ineffective against tumors consisting of a solid mass when transferred after the virus inoculation. When IL was transferred shortly after 500 rad whole-body irradiation of the tumor-bearing mice, tumors regressed markedly and most of them became undetectable, while tumors of other groups receiving normal lymphocytes or medium combined with irradiation ceased to regress soon after the treatment. This effect of IL was abolished by the treatment of IL with anti-Thy 1 antibody and complement, and was not observed against antigenically distinct syngeneic tumors (Meth-A). Concomitant transfer of spleen cells from mice bearing progressing tumors with IL partially impeded the effect of IL. These results suggest that specific immune T lymphocytes induce tumor regression when transferred after the whole body irradiation of the tumor-bearing mice. The effects of irradiation may be divided into two categories: the direct effect on tumor cells, and the indirect effect upon the activity of IL. (Author abstract) (30 Refs)

39. IMMUNOTOXICOLOGY STUDIES ON LEAD: EFFECTS OF EXPOSURE ON TUMOR GROWTH AND CELL-MEDIATED TUMOR IMMUNITY AFTER SYNGENEIC OR ALLOGENEIC STIMULATION.

Kerkvliet NI, Baecher-Steppan L
Sch. Veterinary Medicine, Oregon State Univ., Corvallis, OR, 97331
Immunopharmacology; 4(3):213-224 1982

Chronic exposure of C57Bl/6 mice to lead acetate in drinking water enhanced growth of primary Maloney sarcoma virus (MSV)-induced tumors. In a subsequent continued survival study, exposed mice showed a decrease in late-appearing progressive tumors. Cell-mediated cytotoxic response in spleen or lymph nodes of tumor-bearing mice was significantly augmented by lead exposure. Further studies in an allogeneic tumor model and studies of macrophages from lead-exposed mice suggest significant impairment of macrophage function by lead. (33 Refs)

OTHER RELATED STUDIES

40. BURKITT'S LYMPHOMA.

Ziegler JL
Veterans Admin. Medical Center, San Francisco, CA
CA; 32(3):144-161 1982

Etiology, clinical features, staging, treatment, and immunology of Burkitt's lymphoma are reviewed. Most, but not all cases are associated with Epstein-Barr virus (EBV); the causative role of EBV, if it exists, may be related to differences in viral strains. In addition to EBV, genetic factors, immunoregulatory determinants related to environment, and possibly an RNA virus have also been suggested as causes. Systemic chemotherapy is the treatment of choice. After complete remissions lasting about 1 yr, recurrence is rare. Prognosis is directly related to the tumor burden upon initial presentation. Burkitt's lymphoma is one of a dozen neoplasms that can be cured by drugs alone. It is the most likely candidate for a virus-induced human tumor. Studies of the association of Burkitt's lymphoma and EBV led to the discovery of EBV as the cause of infectious mononucleosis. Experimental and clinical studies of Burkitt's lymphoma have led to important advances in immunobiology and tumor immunology. Promising approaches in immunotherapy include rapid removal of antigen excess and immune complexes from the circulation and enhancement of normal immunoregulatory controls of the body. (121 Refs)

41. EFFECTS OF ADRENAL CORTICAL STEROIDS AND OSMOTIC BLOOD-BRAIN BARRIER OPENING ON METHOTREXATE DELIVERY TO GLIOMAS IN THE RODENT: THE FACTOR OF THE BLOOD-BRAIN BARRIER.

Neuwelt EA, Barnett PA, Bigner DD, Frenkel EP
Dept. Surgery (Div. Neurosurgery), Biochemistry, Oregon Health Sciences Univ., Veterans Admin. Medical Center, Portland, OR, 97201
Proc Natl Acad Sci USA; 79(14,part1):4420-4423 1982

The effect of adrenal cortical steroids and osmotic blood-brain barrier modification on methotrexate delivery to normal and glioma-bearing rats was studied. In animals with the avian sarcoma virus-induced glioma, osmotic blood-brain barrier modification resulted in significantly increased delivery of methotrexate to the tumor-bearing hemisphere (including the tumor, the brain around the tumor, and the brain distant to the tumor), compared to the nonmodified hemisphere or to control animals. The administration of adrenal steroids, followed by intracarotid methotrexate, resulted in slightly decreased chemotherapeutic agent (methotrexate) delivery to the tumor, the brain around the tumor, and the brain distant to the tumor. When adrenal steroids were given prior to barrier modification and methotrexate therapy, the level of methotrexate was significantly less in the tumor. These studies provide evidence that the blood-brain barrier exists in tumors and is a factor in drug delivery to tumors. Steroid administration greatly interferes with the enhancement of drug delivery to tumors that can be achieved with osmotic blood-brain barrier modification. (Author abstract) (17 Refs)

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